New diagnostic and research techniques in allergic rhinitis and chronic rhinosinusitis

Sokolowska, Milena ; Akdis, Cezmi A

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GLOBAL ATLAS OF

ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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Allergic rhinitis - mechanisms

Allergic rhinitis - epidemiology and risk factors

Allergic rhinitis - clinical features and co-morbidities

Allergic rhinitis - diagnosis

Allergic rhinitis - treatment

Allergic rhinitis - Special considerations

Chronic rhinosinusitis (CRS) – mechanisms, epidemiology, risk factors and co-morbidities

Chronic rhinosinusitis - diagnosis and management

Towards a comprehensive global strategy for the management of allergic rhinitis and chronic rhinosinusitis

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PREFACE

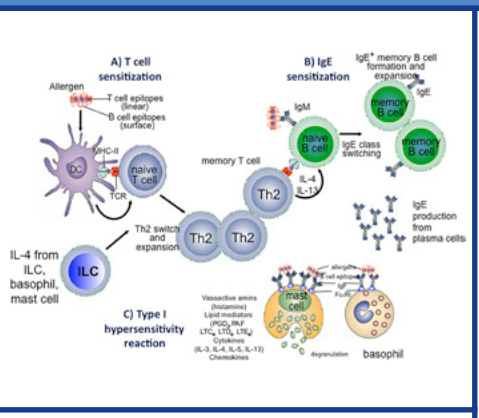
The World Health Organization declares chronic respiratory diseases as one of the 4 major health problems of mankind. Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) affect more than 30% of the population worldwide. The socio-economic impact of chronic upper airway diseases is estimated in Europe with more than 150 billion Euro per year. Unmet needs in the field of AR and CRS can be identified in several domains: education, research, development and clinical care. In addition, the huge socioeconomic burden of AR and CRS to health care systems is expected to substantially increase in the future, warranting new policies in healthcare at the global and national level.

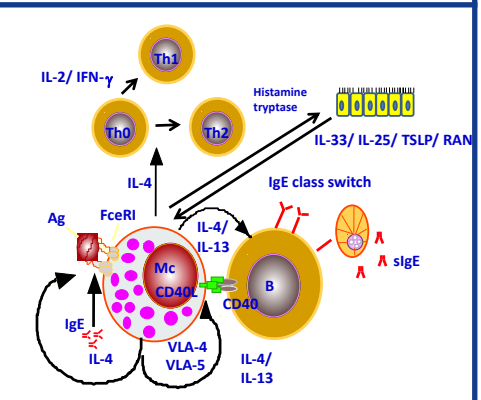
To tackle the huge global health problem of chronic upper airways inflammation, the EAACI decided to develop the "Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis" as a follow up of the "Global Atlas of Allergy" and "Global Atlas of Asthma" which were launched in 2013 and 2014, had a huge success worldwide, and are currently translated into several languages. With this Atlas, EAACI and the authors of the Atlas aim to increase awareness on the global epidemic and the burden of chronic inflammatory upper airways diseases and to bring to the global attention the need to be recognized as a main concern in national health strategies; to reinforce the role of early diagnosis and treatment, education and prevention in a structured management strategy; to reveal their priority for research; to provide guidance on how to overcome barriers; to expand the existing programs and tools and explore innovative solutions for a comprehensive global management approach.

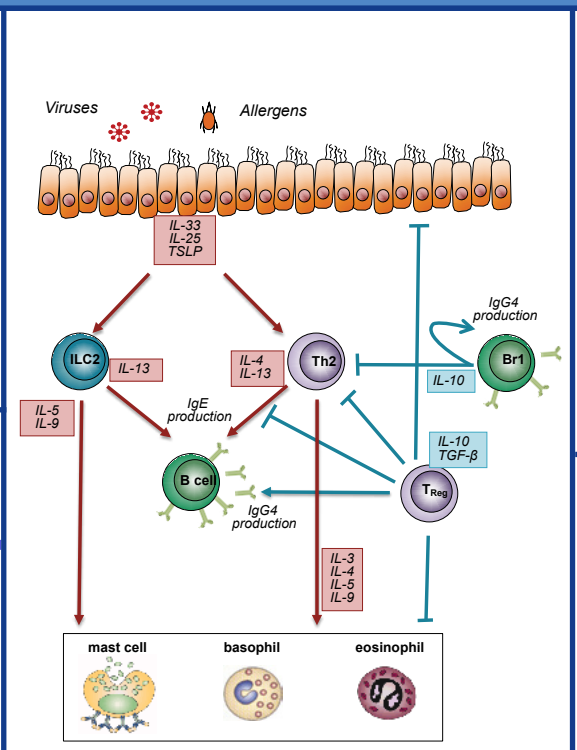
The EAACI Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis contains 154 chapters written by 218 authors with 269 illustrations and 92 tables. It is developed as a desktop reference for multisectoral usage covering all aspects of AR and CRS from epidemiology, risk factors and molecular and cellular mechanisms to their management, clinical features and co-morbidities, diagnosis, treatment, prevention and control. In addition, the Atlas will offer an educational tool and a desktop reference for medical students, allied health workers, primary care physicians, pharmacists, medical industry, policy makers, patient organizations and specialists dealing with AR and CRS. We would like to thank all of the authors for their contributions.

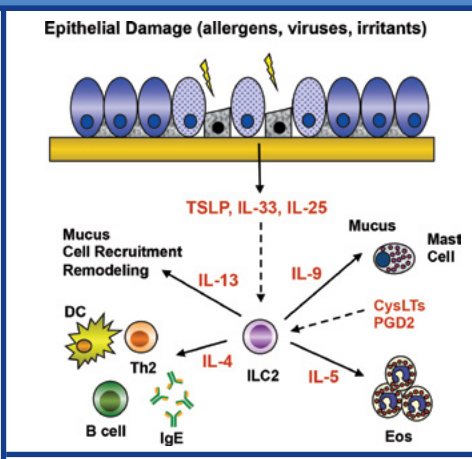
Cezmi A. Akdis
Peter W. Hellings
Ioana Agache
Editors

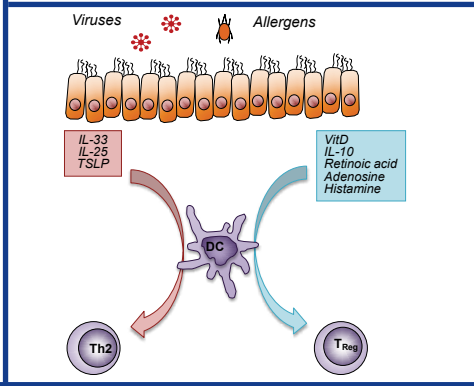
Section A











ALLERGIC RHINITIS - MECHANISMS

- What is allergic rhinitis
- The underlying mechanisms in allergic rhinitis
- The innate immune response in allergic rhinitis
- Mast cell in allergic rhinitis
- Basophils in allergic rhinitis
- Innate lymphoid cells in allergic rhinitis
- Natural killer (NK) and NK-T cells in allergic rhinitis
- The immune response in tonsils
- Eosinophils in allergic rhinitis
- Antigen presenting cells in allergic rhinitis
- The role of T- and B-lymphocytes in allergic disease
- Cytokines and chemokines in allergic rhinitis
- Local and systemic IgE in allergic rhinitis
- IgE repertoires in allergic rhinitis
- MicroRNAs in allergic rhinitis and chronic rhinosinusitis
- Regulation of inflammation by cell death in allergic rhinitis
- Mechanisms of immune regulation in allergic rhinitis
- Lipid mediators in allergic rhinitis: inflammation and resolution of inflammation
- The epithelial barrier in the nose
- Neuro - immune mechanisms in allergic rhinitis
- Nasal hyperreactivity
- Animal models of allergic rhinitis

1 WHAT IS ALLERGIC RHINITIS

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KEY MESSAGES

- Allergic rhinitis (AR) is a symptomatic IgE-driven inflammation of the nasal mucosa
- Nasal congestion/obstruction, rhinorrhoea, itchy nose and/or eyes, and/or sneezing are the symptoms of AR
- Allergen-specific IgE and eosinophilic inflammation are key features of allergic rhinitis
- AR is often associated with conjunctivitis and asthma
- AR is a risk factor for asthma
- A significant percentage of AR patients remains uncontrolled despite adequate treatment

Allergic rhinitis represents an inflammatory disorder of the nasal mucosa initiated by an allergic immune response to inhaled allergens in sensitized individuals. The allergic immune cascade in the nasal mucosa may give rise to the following symptoms in a variable degree of severity and duration: nasal congestion/obstruction, rhinorrhoea, itchy nose and/or eyes, and/or sneezing. General symptoms like fatigue, impaired concentration and reduced productivity are all associated with allergic rhinitis.

The following criteria are utilized to define rhinitis: the presence of 2 or more nasal symptoms for more than 1 h per day. The discrimination between mucosal and anatomic problems giving rise to nasal symptoms is a clinical judgement based on a proper clinical examination of the nose and endonasal cavity (Figure 1). A history with 2 nasal symptoms suggestive of AR, with confirmation of nasal inflammation by clinical examination and diagnostic tests showing sensitization to inhalant allergens, is the cornerstone of the diagnosis.

The new nomenclature on classification of hypersensitivity / allergic diseases for ICD-11 by crowd-sourcing the allergists community, is currently proposing specific definitions for subtypes of rhinitis. Based on history and clinical examination supplemented by diagnostic tests, rhinitis patients are classically divided into different phenotypes: 1/ allergic, 2/ infectious, 3/ non-allergic, non-infectious, and 4/ mixed rhinitis (Figure 1). In a recent TF of the ENT section of EAACI, different rhinitis subtypes are being distinguished (Figure 1).

The allergic immune response involves a nasal as well as systemic immune response. The systemic nature of the allergic immune response with increased levels of IgE, IL-5 and blood eosinophilia has been recognized for several decades. In addition to nasal symptoms, inhalation of airborne allergens may give rise to conjunctival symptoms like itchy eyes, tearing, congestion of the conjunctival vessels, chemosis and periorbital oedema. Allergic rhinitis may be a predisposing factor to develop disease in adjacent organs like the paranasal sinus cavities, middle ear, nasopharynx and larynx. In view of the consideration of allergic rhinitis and asthma being part of the airway allergy syndrome, we have nowadays good insight into the epidemiologic association between AR and AA, diagnostic requirements for considering the problem of upper or lower airways as one entity, and therapeutic implications for optimal treatment of

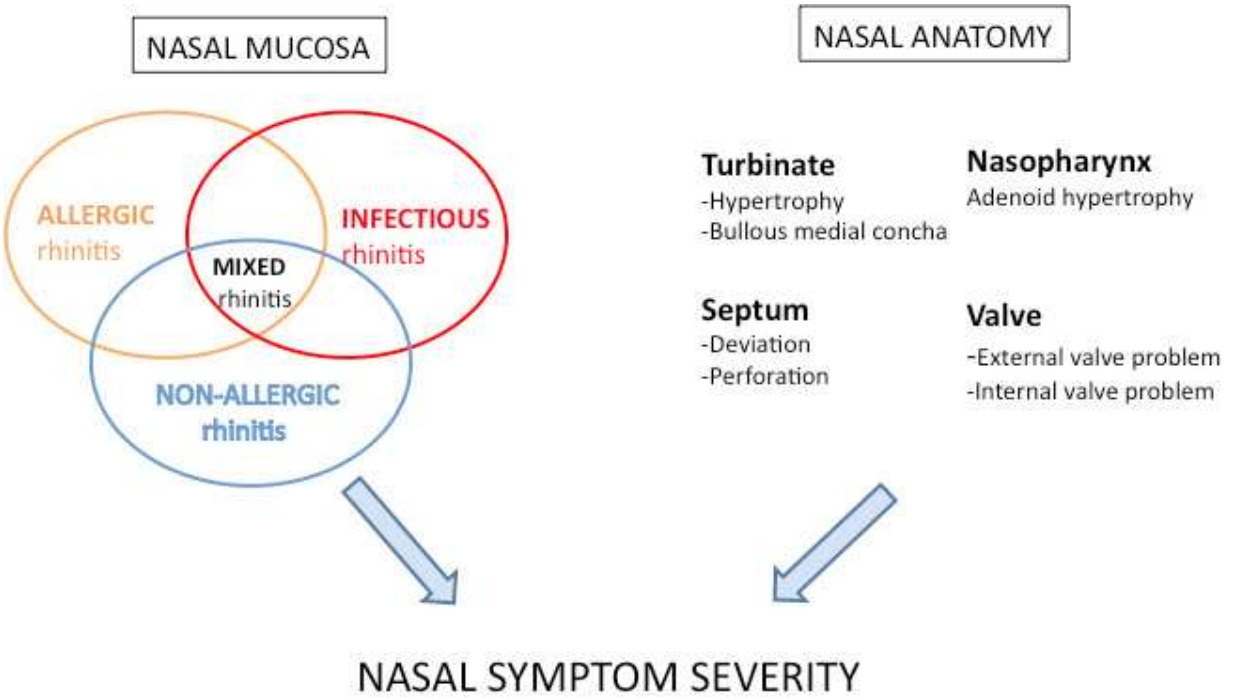

Figure 1 Mucosal and anatomic factors contributing to nasal symptom severity.

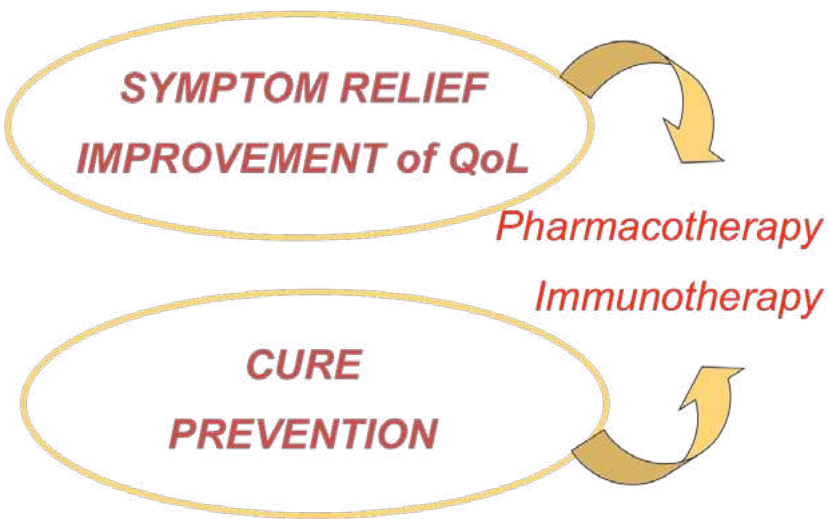

Figure 2 Aims and cornerstones of medical treatment for AR.

AR and AA. Of note, AR is a major risk factor for asthma.

Treatment of AR can be divided into medical treatment aiming at reducing inflammation with improvement of the quality of life, and immunotherapy aiming at inducing tolerance (Figure 2). Successful immunotherapy for Th2 mediated allergic conditions is associated with the induction of IL-10 and TGF-β producing regulatory T (Tr)-1 cells.

The majority of AR patients are well controlled with guideline-based treatment, but up to 20% of AR patients may experience bothersome symptoms despite adequate first-line and second-line treatment (Figure 3). The challenge of AR care in the future will be to optimize care pathways leading to a higher level of symptom control and prevent the progression towards asthma.

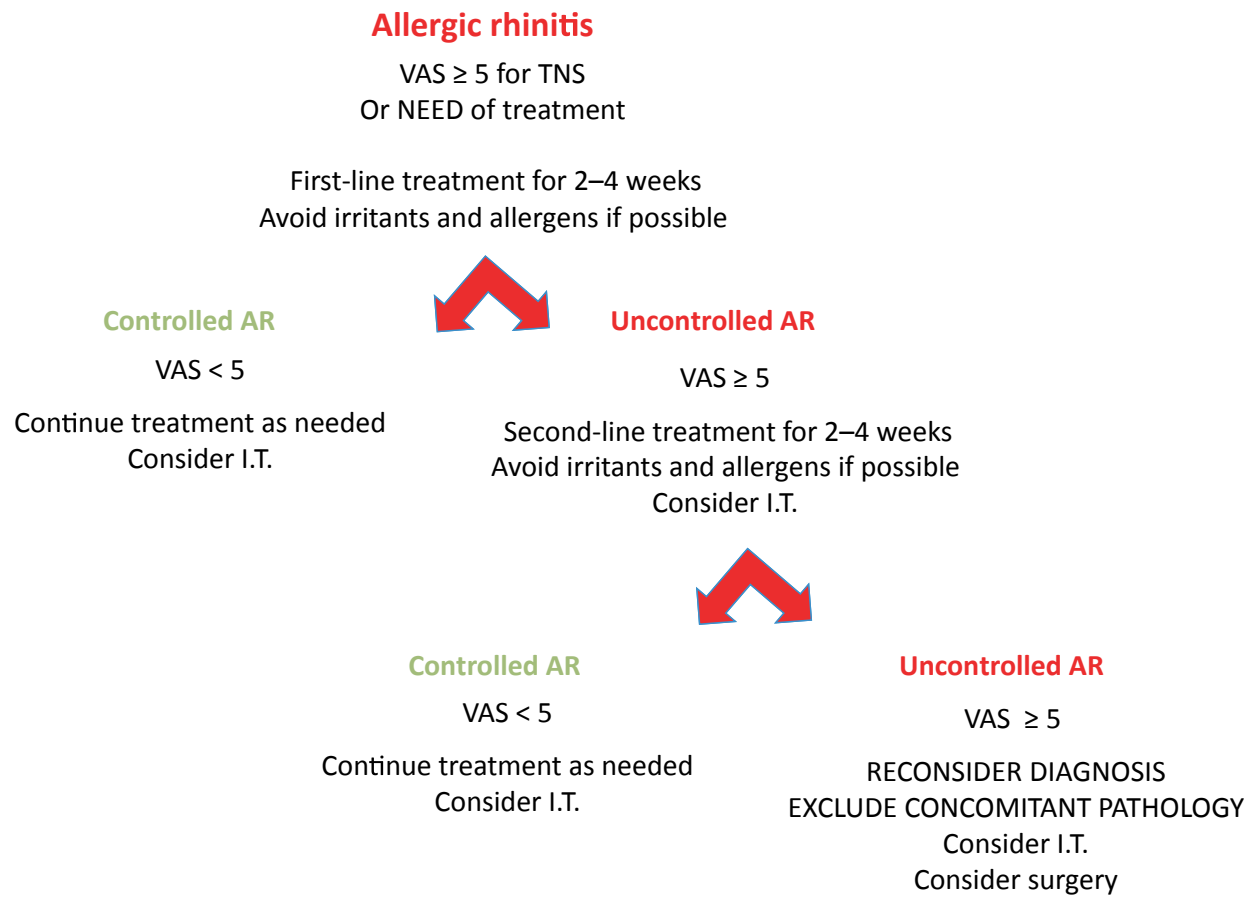

Figure 3 Treatment algorithm of AR including the new concept of AR control.

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2 THE UNDERLYING MECHANISMS IN ALLERGIC RHINITIS

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KEY MESSAGES

- Better understanding of the underlying immune mechanisms in allergic rhinitis (AR) is central to developing improved and more targeted therapies
- Development of the Th2 cell response and of the B cell and allergen-specific IgE response represent the sensitisation phase
- A type 2 immune response including T cells, innate lymphoid cells, local eosinophils and IgE are important players
- An IgE-mediated mast cell degranulation upon exposure to allergens represents the early response
- A late-phase response is characterized by recruitment of T cells, eosinophils and basophils
- Local IgE production without circulating specific IgE can take place
- Epithelial involvement in the type 2 immune response takes place, with the secretion of IL-25, IL-33 and TSLP

Mechanistic studies in allergic rhinitis (AR) have been performed in biopsies, nasal fluid, nasal scrapings and cultures of cells isolated from humans. The data so far is at the level of co-expressions, associations and correlations. Direct evidence for human in vivo relevance has not been demonstrated for many of the below listed findings. Animal models still need to be improved and may not fully represent the human in vivo situation. The most decisive data on mechanisms of AR reflecting human in vivo situation are obtained from therapeutic response to allergen immunotherapy, anti-histamines, corticosteroids as well as response to biologicals, such as anti-IgE and anti-IL-5 monoclonal antibodies.

IgE SENSITIZATION

After allergen exposure through mucosa and skin, allergens are taken up by antigen-presenting cells, processed to T cell epitope peptides and presented to helper T lymphocytes by MHC-class-II molecules (Figure 1). IL-4 released from innate lymphoid cells (ILC), mast cells or basophils and notch, jagged interaction in the dendritic cell and T cell interaction may be important in the initiation and clonal expansion of a Th2 response. This leads to T cell sensitization and memory development. Activated CD4+ T helper 2 lymphocytes release cytokines, mainly IL-4 and IL-13 and interact with B lymphocytes to induce the class-switch and synthesis of allergen-specific IgE (IgE sensitization) and development of IgE B cell memory and IgE-secreting plasma cells. Allergen-specific IgE binds to the high affinity receptor for IgE (FcεRI) on the surface of mast cells. The presence of circulating IgE towards a specific allergen is not fully linked to a clinically significant AR, and levels of total IgE rarely provide information about IgE to specific allergens.

EARLY PHASE (IMMEDIATE) RESPONSE

The early or immediate phase response occurs in IgE-sensitized individuals within minutes of exposure to the allergen and lasts for about 2-4 hours. Mast cell degranulation is a cardinal component of the early phase response. Mast cells are abundant in the epithelial compartment of the nasal

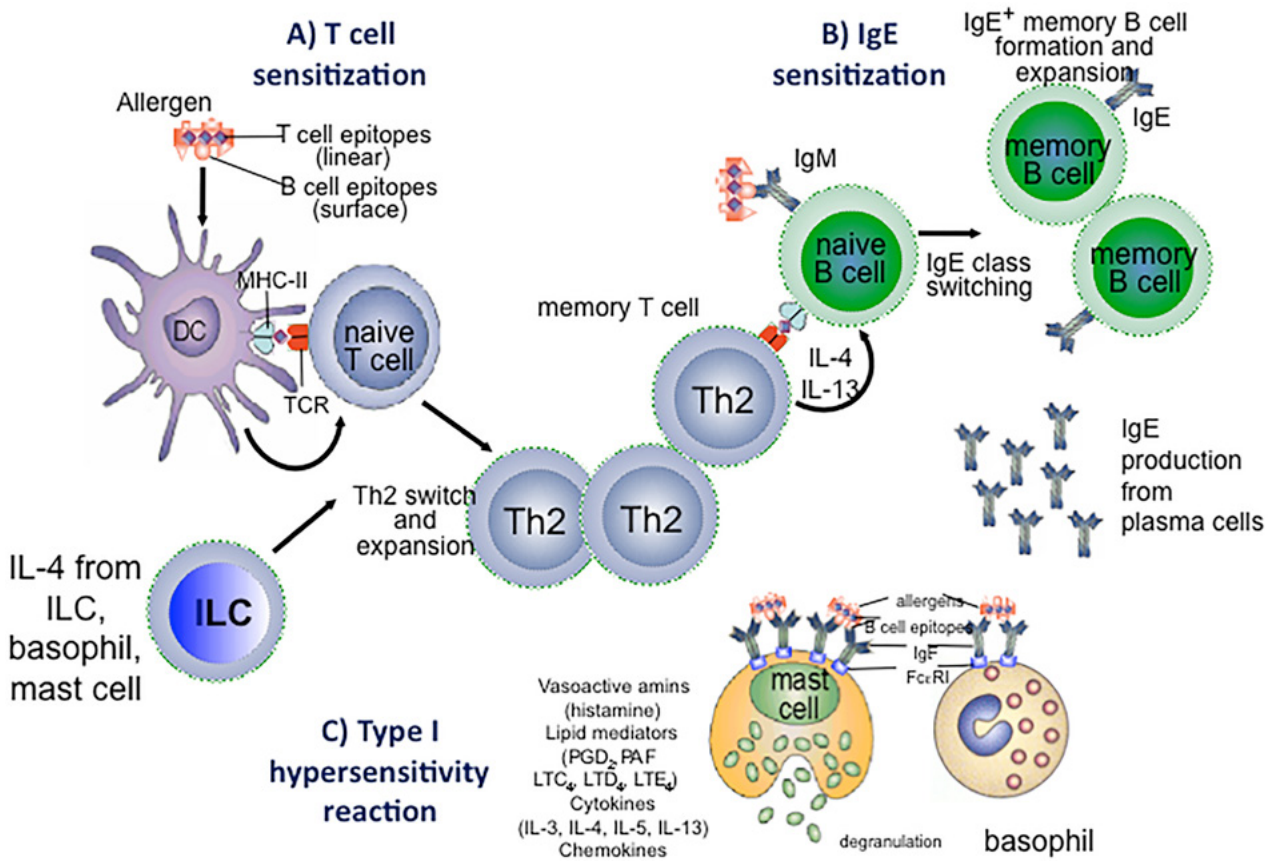

Figure 1 Sensitization and type I hypersensitivity reaction. A) T cell sensitisation, clonal expansion and memory Th2 cell development after allergen presentation to T cells, B) IgE sensitization after Th2 cell naïve B cell interaction, C) Type I hypersensitivity reaction after cross-linking of the FcεRI bound IgE molecules by allergens on mast cells.

mucosa and can be easily activated upon re-exposure to the allergens. Upon allergen cross-linking of specific IgE bound to the surface high affinity receptors (FcεRI) of mast cells degranulate and release a variety of pre-formed and newly synthesized mediators leading to the early phase response. Mast cell secretory granules contain preformed mediators that are rapidly (within seconds to minutes) released into the extracellular environment. These mediators include histamine, leukotrienes, prostaglandins, proteases, proteoglycans, cytokines and chemokines. They are responsible for mast cell-mediated allergic reactions, including edema, increased vascular permeability and nasal discharge in AR. Histamine, the major mediator of AR, stimulates the sensory nerve endings of the trigeminal nerve and induces sneezing and pruritus. Histamine also stimulates the secretion of mucous and nasal discharge, and histamine, leukotrienes and prostaglandins act on the blood vessels causing nasal congestion.

LATE PHASE RESPONSE

4-6 hours after allergen stimulation, the early phase response is usually followed by the late phase response. The late phase response lasts for about 18-24 hours and is characterized by influx of T lymphocytes, basophils and eosinophils in the nasal submucosa. Several mediators released by these cells include leukotrienes, kinins, histamine, chemokines and cytokines, which result in the continuation of the symptoms. The production and release of a variety of cytokines such as IL-4, IL-5, IL-9 and IL-13 from mast cells, ILC, basophils and Th2 cells play a role in the orchestration and continuation of the late phase response. IL-4 and IL-13 can upregulate the expression of vascular cell adhesion molecule 1 on endothelial cells facilitating the infiltration of the nasal mucosa with eosinophils, Th2 lymphocytes and basophils. In addition, chemokines, such as RANTES, eotaxin, monocyte

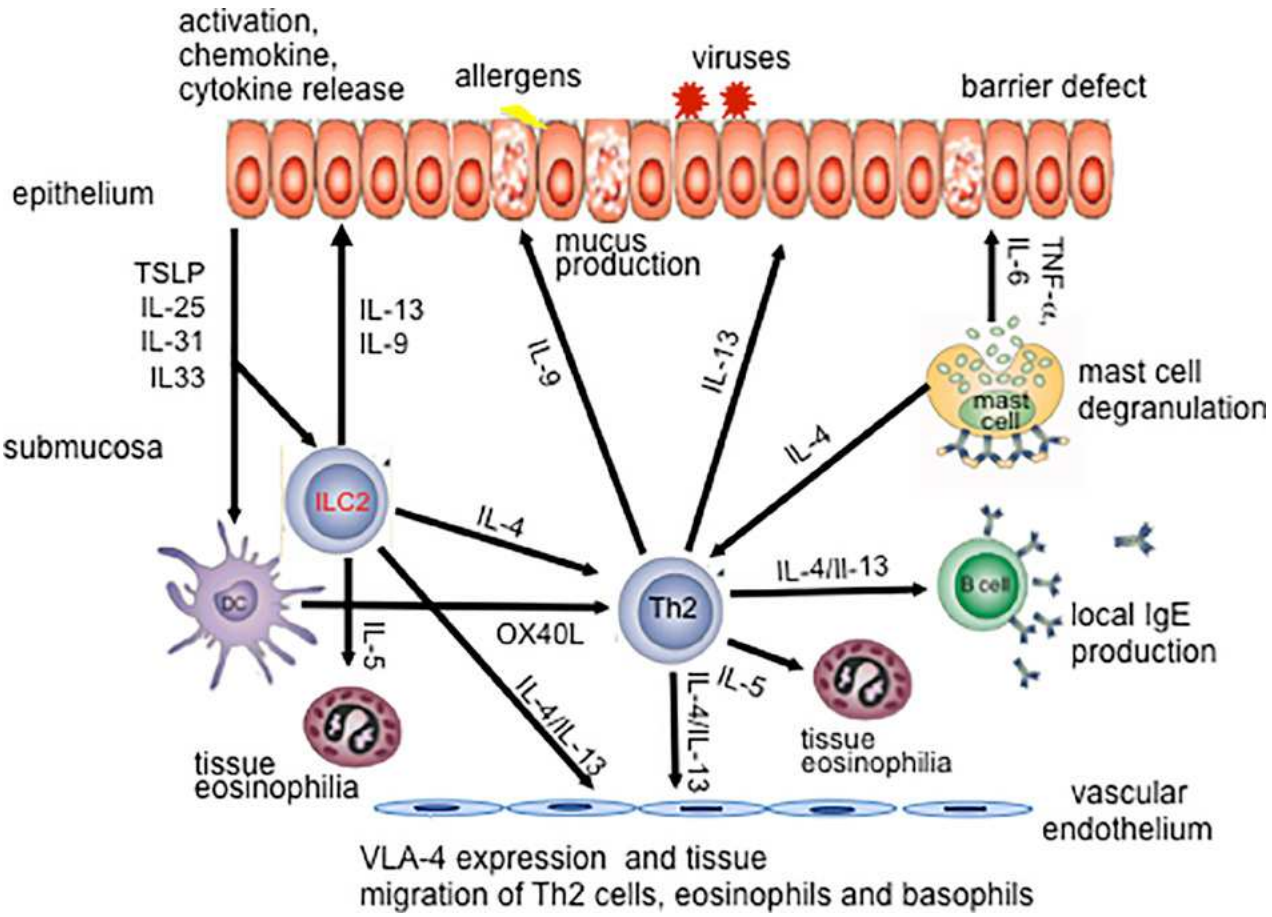

Figure 1 Type 2 inflammation and cytokine network in the AR nose. AR inflammation develops as a combination of innate and adaptive immune response and involvement of resident tissue cells. Epithelial activation and cytokine release (TSLP, IL-25, IL-31, IL-33) leads to type 2 innate lymphoid cells (ILC2) activation. IL-4 from mast cells and ILC2s augments the Th2 response. TSLP-induced OX-40-ligand from DC induces a Th2 response. IL-4 and IL-13 lead to B cell activation and local IgE production. IL-5 from Th2 cells and ILC2 promotes tissue eosinophilia. IL-4 and IL-13 activate the endothelium for tissue migration of eosinophils, basophils and Th2 cells. Multiple Th2 (IL-9, IL-13) and pro-inflammatory cytokines (TNF-α, IL-6) released from ILC2, Th2 and mast cells activate the epithelium.

chemoatractant protein (MCP)-4, and thymus-and activation regulated chemokine (TARC) released from epithelial cells serve as chemoattractants for eosinophils, basophils and T lymphocytes. Other cytokines like granulocyte macrophage colony-stimulating factor (GM-CSF), released largely by epithelial cells, and IL-5 from type 2 ILC and Th2 lymphocytes prolong the survival in the nasal mucosa of the infiltrating eosinophils. Other mediators released from the eosinophils such as the eosinophil cationic protein, platelet-activating factor, major basic protein have additional roles in the late phase response. The late phase response is characterized by a prolongation of symptoms - sneezing, rhinorrhea, but most predominant by a sustained nasal congestion. AR also triggers a systemic inflammation besides local inflammation, which can in turn augment inflammation in both the upper and lower airways and explains the link to asthma.

STRUCTURAL TISSUE CELLS IN ALLERGIC RHINITIS

Epithelial cells in AR have a wide range of immunomodulatory activities through the release of eicosanoids, endopeptidases, cytokines and chemokines (IL-6, IL-8, IL-25, IL31, IL-33, TSLP, GM-CSF, TNF-α, RANTES, TARC, eotaxin, stem cell factor (SCF)) and thus contributing to the enhancement of allergic inflammation. Furthermore, nasal epithelial cells in AR release matrix metalloproteinase (MMP)-2, MMP-9 and MMP-13,

which can cleave almost all secreted and cell surface molecules as well as extracellular matrix. Nasal epithelial cells express HLA-DR and CD86 and can present antigen to T cells. Epithelial cell-derived thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 are essential factors in AR. Increased IL-25 can amplify the ongoing allergic inflammation, particularly by augmenting the Th2 type inflammation. IL-33 can amplify Th2 and particularly the IL-5, IL-9 and IL-13 secreting type 2 ILC activation. All three cytokines can directly and indirectly enhance innate lymphoid cell-contribution to effector functions such as tissue eosinophilia and increased Th2 response (Figure 2).

Epithelial barrier and tight junction integrity is essential in AR as it is in asthma, chronic rhinosinusitis (CRS) and atopic dermatitis. In all these diseases the epithelial barrier is prone to be impaired by allergens and pollutants. With its cysteine protease activity Der p 1 is able to alter the epithelial tight junctions, thereby increasing epithelial permeability. Due to their enzymatic proteolytic activity many allergens can directly activate epithelial cells and can induce cytokine and chemokine release and thus airway inflammation independent of IgE. Furthermore, in AR individuals epithelial cells are more sensitive to air pollutants like diesel exhaust particles.

Endothelial cells play a role in the pathogenesis of AR by participating in the recruitment of leukocytes to the site of the allergic response. Endothelial cell VCAM-1 is over expressed during the pollen season. Endothelial cells in AR are also an important source of several cytokines and chemokines like RANTES and eotaxin. Moreover, similar to epithelial cells, endothelial cells also express the H1 receptor and stimulation with histamine induces activation of these cells.

Tissue macrophages and dendritic cells also contribute to AR inflammation by releasing macrophage-derived chemokine that attracts Th2 cells.

Tissue fibroblasts are also involved in AR. IL-4 promotes the proliferation of allergic fibroblasts, and the production of GM-CSF and SCF increases by histamine stimulation.

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3 THE INNATE IMMUNE RESPONSE IN ALLERGIC RHINITIS

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KEY MESSAGES

- Microbial pattern recognition represents an important task of the innate immune system in the upper airways
- Resident cells (macrophages, dendritic cells, epithelial cells, and mast cells) contribute to microbe and allergen recognition
- The tissue infiltrating celllular response of the innate immune system mainly consists of neutrophils and NK-cells
- Microbes either amplify the inflammatory response or may prevent the development of allergic rhinitis in the context of the "hygiene hypothesis"
- The underlying mechanisms of pro- and anti-allergic immune responses are still not fully elucidated

An important function of the innate immune system in the upper respiratory tract is the recognition of microbial patterns. Several strategies have evolved in order to fulfill this task such as secreted molecules (e.g. anti-microbial peptides, collectins, surfactant proteins, pentraxins), membrane bound receptors (e.g. toll-like receptors, C-type lectin receptors), cytosolic receptors (e.g. NOD-like receptors, RIG-I, MDA5) as well as receptors, which are both secreted or membrane-bound (prototypic examples, CD14 and LPS-binding proteins) (Table 1). These molecules are produced by a variety of resident and non-resident, infiltrative cells in the upper respiratory tract including epithelial cells, dendritic cells (DCs), macrophages, and mast cells. DCs can be subdivided into classic myeloid (mDC) and plasmocytoid (pDC) types which are thought to originate from a common DC-precursor in the bone marrow. mDCs form of subepithelial web, they are rich in pattern-recognition receptors and, therefore, sensitive to microbes, inflammation, and cellular stress. pDCs are particularly relevant for the anti-viral responses, they are expressing TLR7 and TLR9 and release large amounts of interferon-α. Recently, also mast cells (MCs) have been identified as important regulators in the upper airways. MCs express TLR1, TLR2, TLR4, and TLR6, complement receptors for C3a and C5a.

Upon stimulation (microbial, antigen, allergen, or cellular stress) more cells belonging to the innate immune system are recruited. From these cells, innate lymphoid cells will be discussed in detail chapter A6. Neutrophils represent the prototypic circulating phagocyte, which belong to the first line defense mechanism. Another important cell type is the NK-cells exhibiting unique features. They are lymphoid cells, which do not express the classical antigen-specific receptors. NK-cells express a variety of anti-microbial receptors including TLR2, TLR3, TLR4, TLR5, TLR7, and TLR8. NK-cells play a critical role in anti-microbial activities, regulation of apoptosis in target cells, they are producing interferon-γ, TNF-α, but also a variety of TH2-cytokines including IL-5, IL-10, and IL-13. Furthermore, they produce type-I interferon, IL-12, and IL-18.

The cellular network of the innate immune response is important in regulating immune homeostasis in the local tissue. From a functional point of view, microbial encounter may either amplify the inflamma-

TABLE 1

Innate Pattern Recognition Receptors in Humans	
Pattern Recognition Receptors	**PAMP Structures Recognized**
Membrane Bound	
Toll-like receptors	Microbial PAMP's
C-type lectin receptors	
Mannose receptor (CD206)	Microbial mannan
DECTIN-1	β-1,3-Glucan
DECTIN-2	Fungal mannose
DC-SIGN	Microbial mannose, fucose
Siglecs	Sialic acid-containing glycans
Cytosolic	
NOD-like receptors	Peptidoglycans from gram-negative bacteria
	Bacterial muramyl dipeptides
	Anthrax lethal toxin
	Microbial RNA
	Bacterial flagellin
RIG-I and MDA5	Viral double-stranded RNA
Secreted	
Antimicrobial peptides	Microbial membranes (negatively charged)
α-and β-defensins	
Cathelicidin (LL-37)	
Dermcidin	
RegIIIγ	
Collectins	
Mannose-binding lectins	Microbial mannan
Surfactant proteins A and D	Bacterial cell wall lipids; viral coat proteins
Pentraxins	
C-reactive protein	Bacterial phospholipids (phosphorylcholine)
Secreted and Membrane Bound	
CD14	Endotoxin
LPS-binding protein	Endotoxin
MD-2	Endotoxin

tory response (e.g. *Staphylococcus aureus*) or may prevent the development of allergic inflammation in the context of the "hygiene hypothesis". However, the detailed molecular signals and pathways leading either to augmentation and enhancement or to the prevention of the responses have not been fully elucidated yet. Certainly, further research is needed in this field.

In addition to microbes, many allergens may directly interact with cells of the innate immune system. One prominent example is the structural and functional homology of defined allergenic components with the pattern recognition system (e.g. Der p 2 is a homolog for MD-2; Der p 7, Fel d 1, Mus m 1, and Equ c 1 are homologs for lipid-binding proteins). Furthermore, many allergens exhibit protease activity that is associated with their allergenicity. Examples are Der p 1, Der p 3, and Der p 9.

In conclusion, the innate immune system plays a critical role in the first line interaction between the environment and the host. This includes the interactions with pathogens, immune-regulatory microbes, allergens, and toxins. This first line defense mechanism plays also an important role in orchestrating the subsequent adaptive immune response leading either to tolerance or (chronic) inflammation.

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4 MAST CELL IN ALLERGIC RHINITIS

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KEY MESSAGES

- Mast cells are critical cells in the early phase allergic reaction and are major producers of histamine, leukotrienes and prostaglandins
- Mast cells also produce a variety of inflammatory cytokines and chemokines in allergic rhinitis (AR) that regulate the late phase reaction
- IgE-activated mast cells express high levels of the high affinity IgE receptor (FcεRI), the CD40L, produce IL-4 and IL-13 and induce local IgE synthesis in B cells in the nasal mucosa of the AR patient
- Mast cells can autoactivate themselves via upregulating the FcεRI by IgE or IL-4 and thus amplify the ongoing inflammation via the IgE-FcεRI cascade

Mast cells (MCs) have been conventionally known to play a crucial role in the immediate phase allergic reaction (Figure 1). However, over the last 20 years studies focused on nasal and bronchial MCs have clearly shown their wider involvement in ongoing inflammation in AR and asthma. More recent human studies implicate an important role for MCs also in other airway diseases such as chronic obstructive pulmonary disease, respiratory infections and lung fibrosis. While their roles mainly include immune-modulatory, pro-inflammatory and pro-fibrotic activities, MCs can also downregulate inflammation and participate in the defense against respiratory infections.

Human MCs were classified into two phenotypically distinct subpopulations based on the type of neutral proteases they express, namely MC (T) that contain only tryptase, and MC (TC) that contain chymase, cathepsin G and carboxypeptidase in addition to tryptase. In patients with AR, MC (T) are found to abundantly accumulate in the epithelial compartment of the nasal mucosa. Among the factors that induce the selective accumulation of MCsls into the allergic nasal epithelium, Nilsson et al. have suggested stem cell factor (SCF), Salib et al. suggested TGF-β I and more recently Ozu et al. have shown that RANTES is the key molecule regulating the intraepithelial migration of MCs.

Activated MCs release a variety of cytokines such as IL-4, IL-5, IL-6, IL-8, IL-10, IL-13 and TNF-α, express high levels of very-late activation antigen (VLA) 4 and 5 and via interactions with the extra cellular matrix can upregulate cytokine secretion. Such a mechanism may contribute to the enhancement of MCs activation especially when the levels of antigen in the microenvironment are rather low and contribute to nasal hyperresponsivess.

The local production of IgE in the nasal mucosa of AR patients is well established. Cytokines like IL-4, and IL-13 released from T cells help drive B cells toward IgE synthesis and can contribute to the local IgE synthesis and MCs can orchestrate ongoing allergic inflammation (Figure 2). Furthermore, IgE and IL-4 can upregulate the FcεRI expression in MCs. The augmented FcεRI can bind increased number of IgE-Ag complexes, which in turn can enhance the sensitivity of MCs to allergen

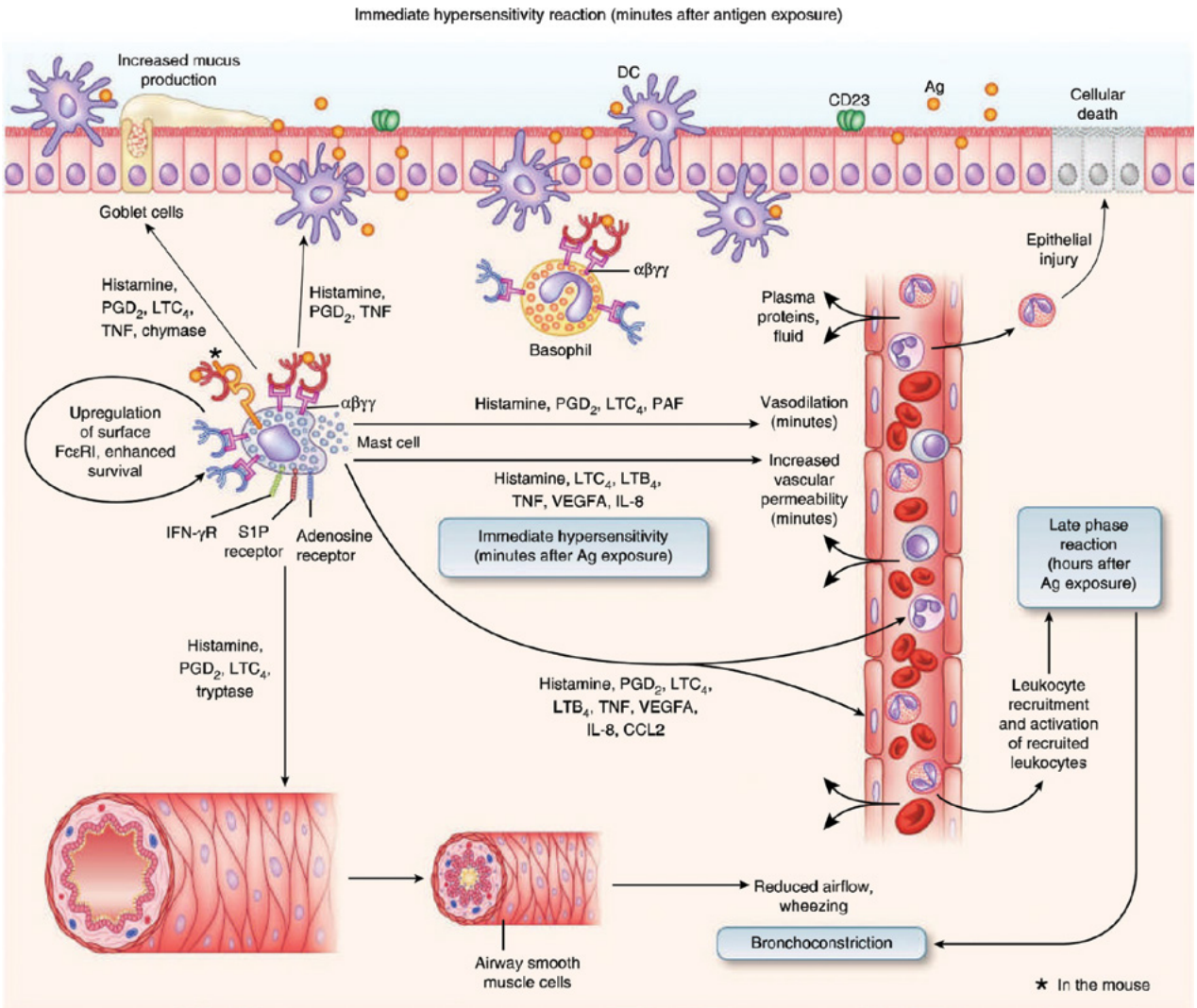

Figure 1 Mast cells and the immediate hypersensitivity reaction.

resulting in the enhancement of the production of immunomodulatory cytokines and chemical mediators, leading to a positive-feedback amplification loop involving the IgE-IgE receptor mast cell cascade. More recently, it has been shown that oxidative stress may upregulate the IL-4 gene expression in mast MCs. MCs can also interact with structural cells, such as epithelial cells and activate these cells or be activated by these cells via cytokines like IL-25, IL-33 and chemokines like RANTES.

There are several therapies targeting MCs for AR. With MCs being the major producers of histamine, leukotrienes and prostaglandins (e.g. prostaglandin D2), the clinical efficacy of antihistamines, anti-leukotrienes in AR can be interpreted as a strong indication of a significant mast cell role in AR. The pioneering drug in this context, the anti-IgE monoclonal antibody omalizumab, has been shown to reduce both inflammatory parameters, as well as patient-related outcomes (e.g. symptom scores and quality of life) in asthmatics and in patients with AR (although omalizumab is not indicated in AR alone).

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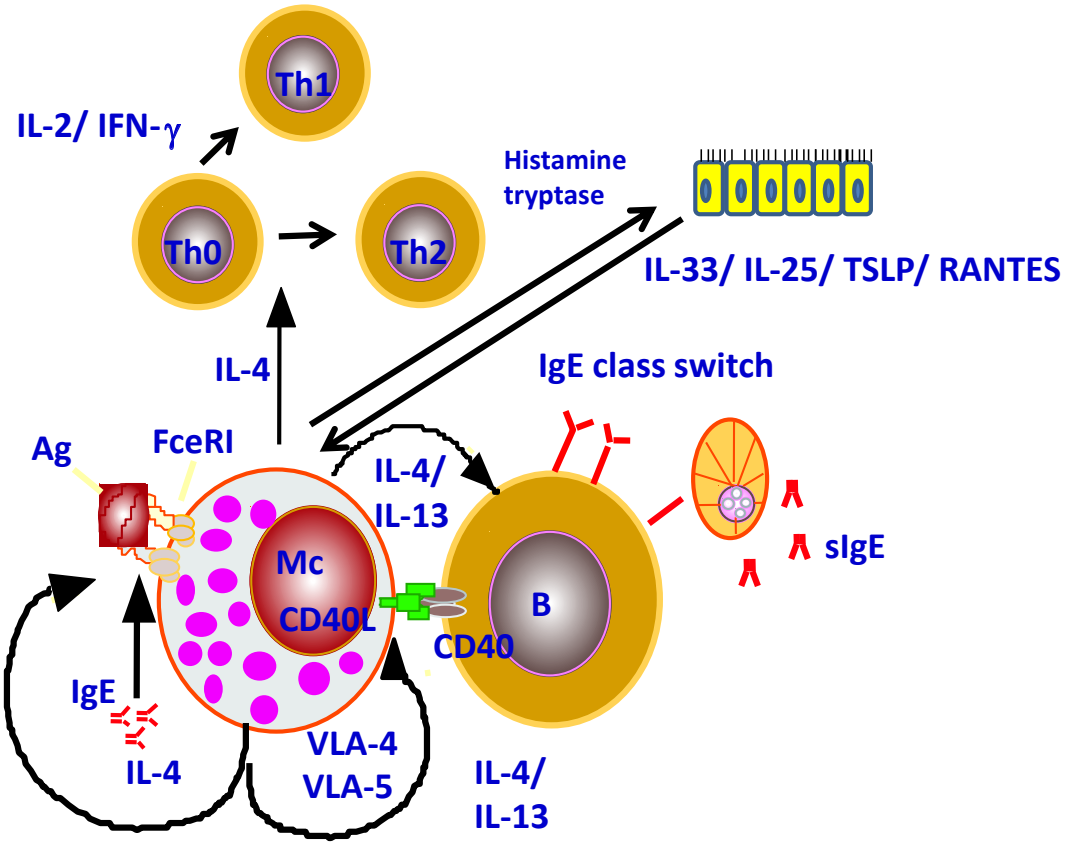

Figure 2 Mast cells orchestrate the ongoing allergic inflammation in AR: under allergic inflammatory conditions, "primed" MCs produce IL-4 and IL-13 and express high levels of the high affinity receptor for IgE and the ligand for the surface antigen CD40, involved in T/B cell interactions leading to IgE production. IL-4 from MCs cells can direct uncommitted helper T lymphocytes toward Th2 and also upregulate the FcεRI expression in MCs and basophils.

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5 BASOPHILS IN ALLERGIC RHINITIS

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Basophils are rare leukocytes that mature in the bone marrow and are released as mature cells in the peripheral blood. Basophils share many properties with mast cells, but are from a different lineage and, in general, are more responsive to different types and lower concentrations of stimuli. Most importantly, mast cells are tissue-bound, while basophils represent a population of rapidly migrating leukocytes that infiltrate tissue sites when needed.

KEY MESSAGES

- Basophils are potent effector cells in allergic diseases
- Basophils infiltrate the nasal mucosa during the inflammatory process in allergic rhinitis (AR)
- Products released by basophils in the nasal mucosa retain the inflammatory process
- Treatment of AR directly or indirectly affects basophils activation and presence in nasal mucosa

BASOPHIL PRESENCE IN NASAL MUCOSA IN ALLERGIC RHINITIS

Several studies have demonstrated basophils in the nasal mucosa in allergic rhinitis (AR) patients. The research group at Johns Hopkins University under supervision of Lawrence Lichtenstein, claiming that the nose was the only organ in which you could sample with a pipette, has been pioneering in this area by thorough analysis of mediators and cells in nasal mucosa. In the allergen-induced late-phase reaction, a typical basophil mediator profile and cells representing basophils were found. Other groups using the basophil-specific antibodies BB1 and 2D7 confirmed this increased basophil numbers (Fig-

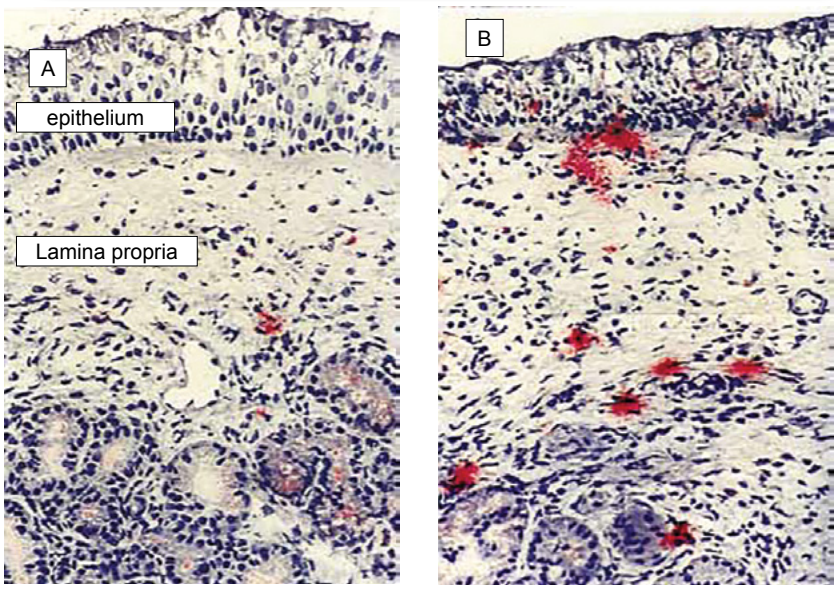

Figure 1 Photomicrograph of basophils (BB1-positive cells (red)) in the epithelium and lamina propria of a nasal mucosa biopsy section obtained from an allergic patient before (A) and 24 hours after (B) allergen provocation. (*Adapted from KleinJan A, McEuen AR, Dijkstra MD, et al. Basophil and eosinophil accumulation and mast cell degranulation in the nasal mucosa of patients with hay fever after local allergen provocation. J Allergy Clin Immunol 2000;106:677-686.*)

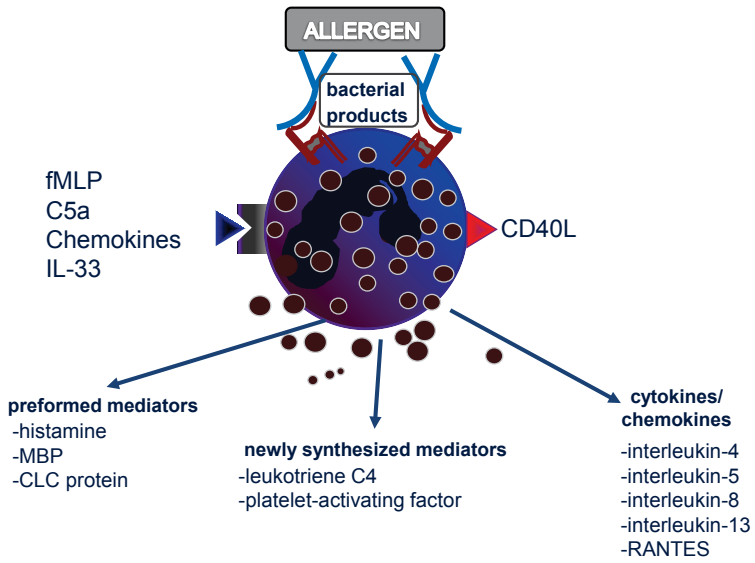

Figure 2 Basophils activation by different type of stimuli. The most prominent activation is via allergen interacting with IgE causing crosslinking of FcεRI. Bacterial products can crosslink IgE independent of its antigen specificity. Other stimuli can stimulate the cells via binding to specific receptors. Activation of basophils results in release of several types of mediators and cytokines/chemokines that are important in allergic diseases, as well as expression of co-stimulatory molecules.

ure 1). Importantly, basophil presence is reduced upon successfully treatment with local steroids or after immunotherapy. Production of chemokines in the nasal mucosa is most likely responsible for the basophil infiltration. The nasal application of the chemokine RANTES/CCL5 leads to influx of basophils.

BASOPHIL PRODUCTS

Basophils are supposed to play an important role via their products released. Next to histamine, basophils can release many pre-formed and newly formed mediators, such as leukotriene C4 and platelet-activating factor. In addition, basophils are potent sources of cytokines and chemokines. An additional mechanism that basophils might use is the stimulation of cells via co-stimulatory molecules. CD40L on basophils will activate local B cells via binding to their CD40 and via simultaneous release of IL-4 might drive local IgE production.

STIMULATION OF BASOPHILS

Although it is unlikely that high levels of allergens will still be present when basophils infiltrate the nasal mucosa, there are several allergen-independent ways that activate basophils (Figure 2). Chemokines are not only important to attract basophils, but also induce their degranulation in higher concentration. Locally produced cytokines will stimulate basophils, either on their own or in combination with other cytokines and mediators, including innate cytokines such as IL-33.

Human basophils, in contrast to their murine counterpart, lack PAR2 receptors, so it is unlikely, if proteases derived from allergens can activate. On the other hand, bacterial products, such as cell wall proteins from *Staphylococcus aureus* and *Peptostreptococcus magnum* can activate basophils via crosslinking IgE, while formyl-methionine-containing tripeptides from microbes can directly activate basophils.

PERIPHERAL BLOOD BASOPHILS IN AR

After nasal allergen challenge basophils from the peripheral blood are stimulated indicating that the local allergic inflammatory process affects also systemically. In addition, AR patients have increased numbers of basophil progenitors in their blood, probably due to continuous release of basophil differentiation factors in the tissue.

In conclusion, basophils and their products can be found in nasal mucosa of AR patients. It is tempting to believe that these cells are important for the pathomechanism in this disease. However, the presence of many other inflammatory cells and their products makes it a challenge to dissect the exact role of basophils in this disease.

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6 INNATE LYMPHOID CELLS IN ALLERGIC RHINITIS

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KEY MESSAGES

- Group 2 innate lymphoid cells (ILC2s) are a recently discovered population of lineage-negative lymphocytes that produce Th2 cytokines
- ILC2s have been detected in human sinonasal tissue and are enriched in eosinophilic nasal polyps from chronic rhinosinusitis patients
- Cat allergen challenge in allergic rhinitis subjects resulted in increased peripheral blood ILC2s
- Peripheral blood ILC2s are increased in pollen-allergic rhinitis patients during pollen season and decreased by subcutaneous immunotherapy

Group 2 innate lymphoid cells (ILC2s) are a recently-discovered population of lymphocytes that produce high levels of Th2 cytokines (IL-4, IL-5, IL-9, IL-13) that promote allergic inflammatory responses in animal models. Human ILC2s are defined by expression of the prostaglandin D2 (PGD2) receptor DP2 (also known as CRTH2) in addition to being lineage-negative (lack surface expression for B, T, NK, and NKT cell as well as mast cell and basophil markers). ILC2s are enriched in nasal polyps from patients with chronic rhinosinusitis (CRS) and are increased in eosinophilic compared with non-eosinophilic polyp endotypes. Unlike conventional T cells, ILC2s are not antigen specific and are activated by several mediators including cytokines TSLP and IL-33, as well as lipid mediators prostaglandin D2 and cysteinyl leukotrienes (Figure 1). Importantly, these mediators have been detected at higher levels in CRS patients and are thus available for ILC2 activation.

Two studies have investigated the effects of allergen exposure on peripheral blood ILC2s in patients with allergic rhinitis (AR). In the first study, changes in peripheral blood ILC2s were assessed four hours after cat allergen challenge in AR subjects with positive cat challenges. The percent of CRTH2+ ILC2s was increased 2-fold after cat allergen challenge compared to diluent control challenge given to the same subjects at a separate visit. The second report demonstrated that peripheral blood ILC2s were increased during grass pollen season in pollen AR patients. Interestingly, the levels of peripheral blood ILC2s were also reduced by subcutaneous immunotherapy. The function of peripheral blood ILC2s after allergen exposure in AR is not known, but may involve recruitment of ILC2s from the bone marrow that are bound for tissues. Importantly, ILC2s express CRTH2 that binds to PGD2 and is known to promote chemotaxis of immune cells including ILC2s. High levels of PGD2 are rapidly produced after airway allergen challenge and could thus promote ILC2 recruitment in AR.

There are currently no studies addressing the role of tissue ILC2s in AR. Whether sinonasal ILC2s are activated after allergen exposure is so far not reported. However, given the capacity for ILC2s to generate large amounts of Th2 cytokines that could propagate chronic inflammation in AR, ILC2s may be a target of future therapy. Additionally, whether human tissue ILC2s are corticosteroid sensi-

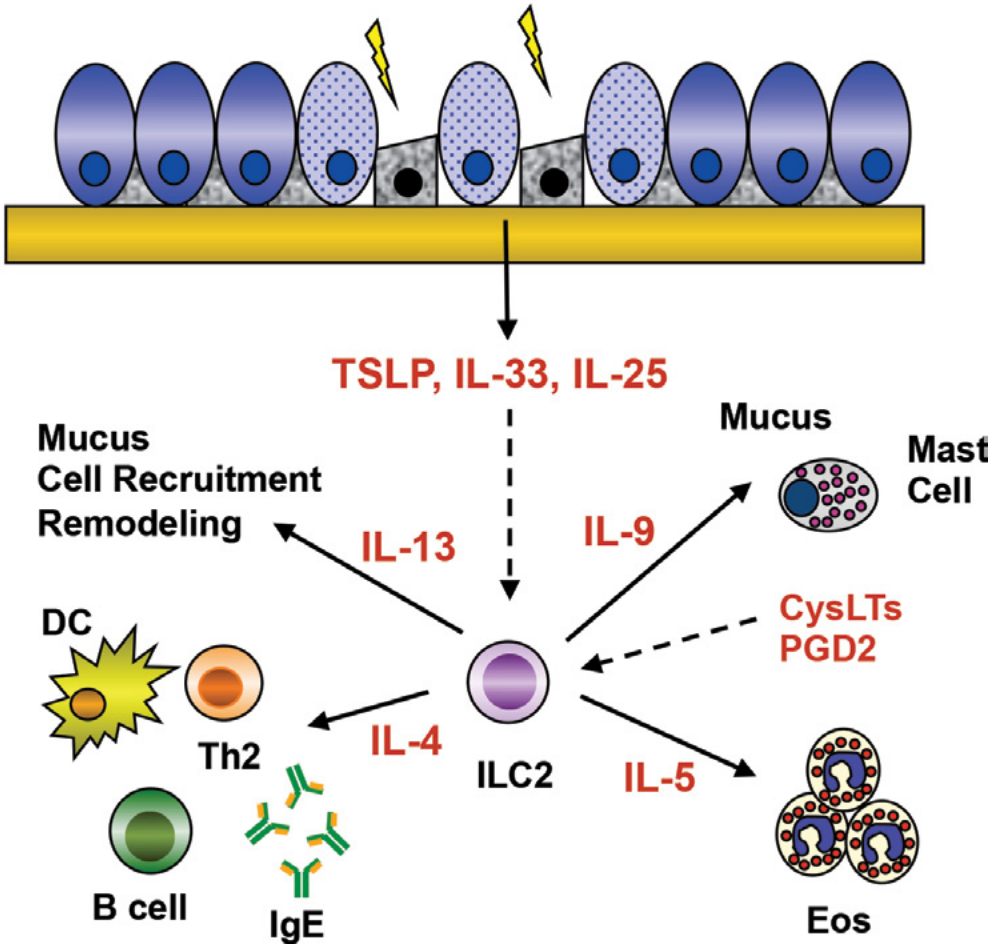

Figure 1 Proposed ILC2 responses in AR. Epithelial damage and activation may occur after exposure to allergens, viruses, or irritants. ILC2s are activated by epithelial cytokines TSLP, IL-33, and IL-25 as well as prostaglandin D2 (PGD2) and cysteinyl leukotrienes (CysLTs) produced by mast cells and eosinophils. In turn, ILC2s produce Th2 cytokines including IL-4, IL-5, IL-9, and IL-13. ILC2 IL-4 production may contribute to differentiation of Th2 cells and promote IgE production by B cells. IL-5 secretion induces recruitment, activation and survival of eosinophils. IL-9 promotes mast cell accumulation and mucus production and IL-13 induces immune cell influx, tissue remodeling and further enhances mucus production. (*Adapted from Doherty TA. At the Bench: Understanding group 2 innate lymphoid cells in disease. J Leukoc Biol 2014;97:455-467.*)

tive is also not known and has significant implications for improved treatment for patients.

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7 NATURAL KILLER (NK) AND NK-T CELLS IN ALLERGIC RHINITIS

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Alterations in the innate immune system cells, as natural killer (NK) cells, NK-T (NK-T) cells, γδ T cells, dendritic cells, and innate lymphoid cells, play a pivotal role in the development and immunomodulation of allergic rhinitis (AR).

KEY MESSAGES

- Inflammation in allergic rhinitis (AR) is partially mediated by the innate immune system
- *In vivo* existence of type 2 cytokine-producing NK cells and increased NK - cytotoxic capacity in patients with AR support the role of NK cells in AR
- Limited findings in NK-T cells suggest that NK-T cells are not directly related to the development of AR, but they may play important roles in the development of chronic sinusitis

NK-CELLS

NK cells not only exert cytotoxic activity against tumor cells or infected cells but also act to regulate the function of other immune cells through secretion of cytokines and chemokines or cell contact-dependent mechanisms. Human NK cells have the capacity to differentiate into two functional distinct subsets, NK1 or NK2, which are analogous to the T-cell subsets Th1 or Th2. In addition, a regulatory NK cell subset has been described that secretes IL-10, shows antigen-specific T-cell suppression, and suppresses IgE production.

The percentage of NK cells and their cytotoxic activity are higher in patients with AR compared with non-atopic subjects. Additionally, patients with atopic respiratory diseases have a higher activity of NK cells. The role of type 2 cytokines in allergic diseases has been established, and NK cells are possibly the source of Th2 cytokines. IL-4^{+} NK cells were significantly higher while IFN-γ^{+} NK cells were non-significantly lower in AR patients compared to healthy non-atopic subjects. IL-13 secretion from NK cells was also significantly higher. These findings confirm the existence of type 2 cytokine-secreting NK cells in AR and show their increased number and enhanced cytotoxicity compared to normal individuals.

In chronic rhinosinusitis, decreased NK cell functions were associated with some poor prognostic factors such as peripheral blood eosinophilia. Thus, NK cells may play an important role in regulating inflammatory process also in chronic sinusitis pathogenesis.

NK-T CELLS

NK-T cells are a unique CD1d-restricted T cells with NK cell surface markers and play important roles in innate immunity. The NK-T cells were detected with varying degrees in the sinus mucosa from asthmatic patients with chronic sinusitis, but not in the nasal mucosa of non-asthmatics nor in the nasal mucosa of patients with AR. NK-T cells might play important roles in the enhanced Th2 cytokine expression and increased infiltration of Th2 cells and eosinophils observed in the sinus mucosa of asthmatic patients with chronic sinusitis through MHC-independent mechanisms. There is evidence that alterations of the NK and NK-T cells are relate to the development and immunomodulation of AR.

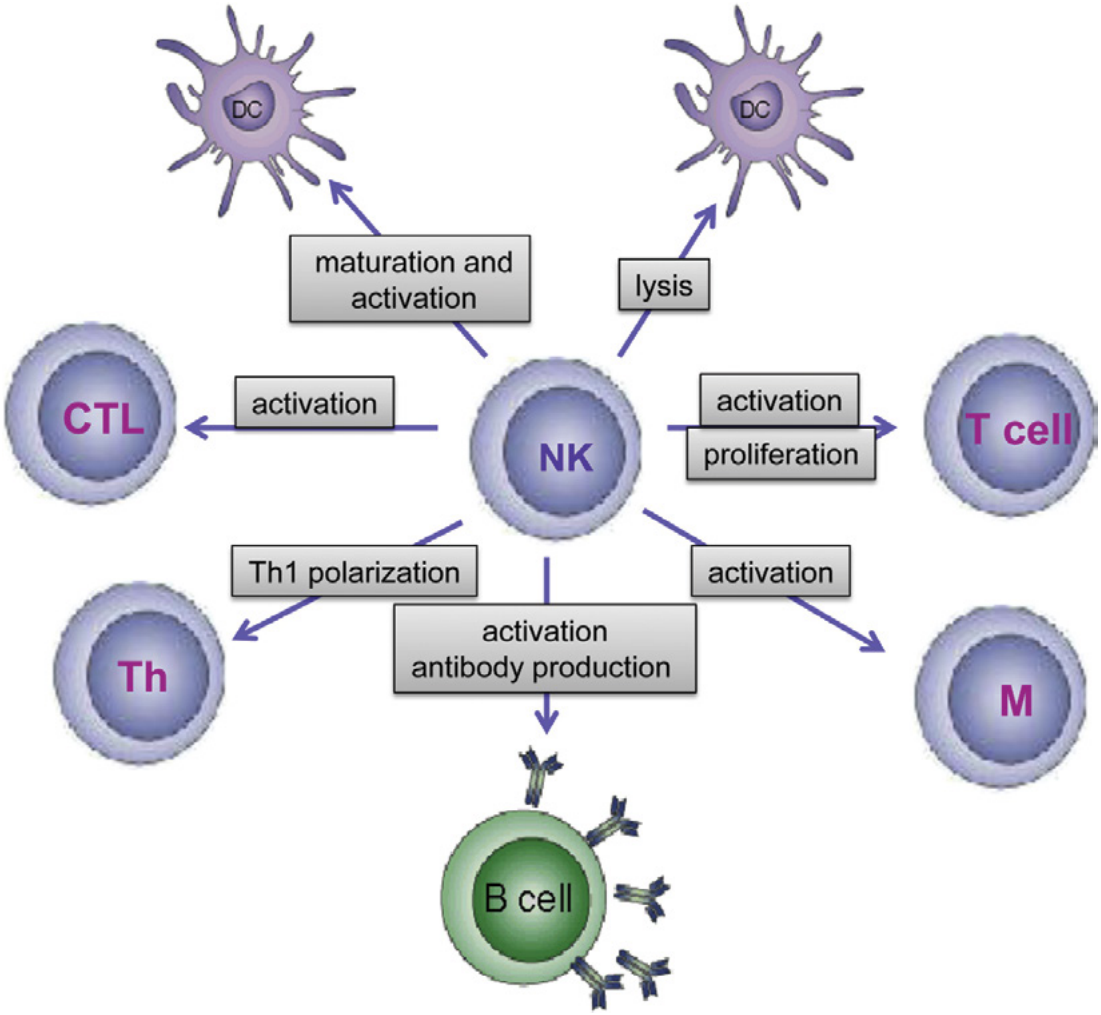

Figure 1 The diagram shows a hypothetical scheme of the potential role of NK cells in the network of immune cells. NK cells play an important role in innate and adaptive immunity, and they can influence the development of dendritic cells (DC) & macrophages (M) and adaptive T- & B-cell immune responses. Cytokines, such as interferon IFN-γ, which are produced by activated NK cells, activate cytotoxic T lymphocytes (CTL) and helper T cell (Th) responses. This leads to the proliferation of helper T cells and cytokine production. Cytokines that are produced by NK cells might also regulate antibody production of B cells. (*Reprinted from J Allergy Clin Immunol, 132/3, Deniz G, van de Veen W, Akdis M. Natural killer cells in patients with allergic diseases, 527-535, Copyright 2013, with permission from Elsevier.*)

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8 THE IMMUNE RESPONSE IN TONSILS

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New human *in vivo* models are needed for allergy and asthma research. Tonsils are secondary lymphoid organs and primary nasopharyngeal lymphoid tissue. The four areas of tonsil tissue in the naso- and oropharynx are shown in Figure 1. Their highly cryptic structure is ideal for sequestering food- and aeroallergens and infectious agents for their first contact with the immune system (Table 1, Figure 2). Palatine tonsils are removed by tonsillectomy without disturbing the integrity of the relatively big lingual tonsil as well as tubal tonsils. Due to their anatomic location, tonsils provide a new *in vivo* model for the understanding of immune response development and immune tolerance induction.

KEY MESSAGES

- Tonsils represent an innovative *in vivo* human model to directly investigate allergen/antigen-specific immune response development
- Functional allergen-specific FOXP3$^+$ Treg cells are identified in tonsils
- Certain innate immune response signals and pro-inflammatory cytokines break allergen-specific CD4$^+$ T-cell tolerance in tonsils
- Tonsillar immune response profile can be influenced by respiratory virus infections, allergic conditions and age and show distinct clusters of immune activation/regulatory versus anti-viral immune response

TABLE 1

Facts about tonsil immunology
Tonsils represent first line lymphatic organs, a fully organized lymphoid tissue with high exposure to aeroallergens, food antigens and to infectious agents
The highly cryptic structure of tonsils sequesters all swallowed or inhaled particles and allows long-term exposure of antigens. The pressure of swallowing further squeezes these particles against tonsil tissue
Tonsils express high levels of allergen-specific T cells, T regulatory cells, plasmocytoid dendritic cells and innate lymphoid cells
Tonsillectomy only removes the palatine tonsils and sometimes adenoids. The lingual tonsil, which is anatomically big, remains intact and is immunologically active lifelong

INDUCTION AND MAINTENANCE OF ALLERGEN-SPECIFIC FOXP3 TREG CELLS IN HUMAN TONSILS

Active regulation of peripheral T-cell repertoire is an essential mechanism for inducing and maintaining tolerance to allergens. The generation of regulatory T (Treg) cells constitutes a main component of oral tolerance induction. Allergen-specific CD4$^+$FOXP3$^+$ T reg cells with suppressive activity exist in human palatine and lingual tonsils. Their frequency is approximately 3 times higher in tonsils compared to peripheral blood. Thus, tonsils have an active role in the first step of oral tolerance induction.

TRIGGERING OF SPECIFIC TOLL-LIKE RECEPTORS AND PRO-INFLAMMATORY CYTOKINES BREAKS ALLERGEN-SPECIFIC T-CELL TOLERANCE IN HUMAN TONSILS

Human tonsils show very low levels of allergen-induced T cell proliferation, thus representing a very suitable *in vivo* model to assess mechanisms of breaking allergen-specific T cell tolerance. During these events dendritic cells (DCs) can control the suppressive activity of Treg cells. Plasmocytoid DCs dominate in both lingual and palatine tonsils. $CD4^+FOXP3^+$ Treg cells co-localize with plasmocytoid DCs and proliferate in T cell areas of tonsils. Triggering of TLR4 or TLR8, as well as IL-1β or IL-6 are able to enhance allergen-specific $CD4^+$ T-cell responses in human tonsils. Myeloid DCs is the main DC subset mediating such effects, whereas plasmocytoid DCs or other innate stimuli (such as stimulation of TLR-7 and TLR-9) do not show any tolerance-breaking effect.

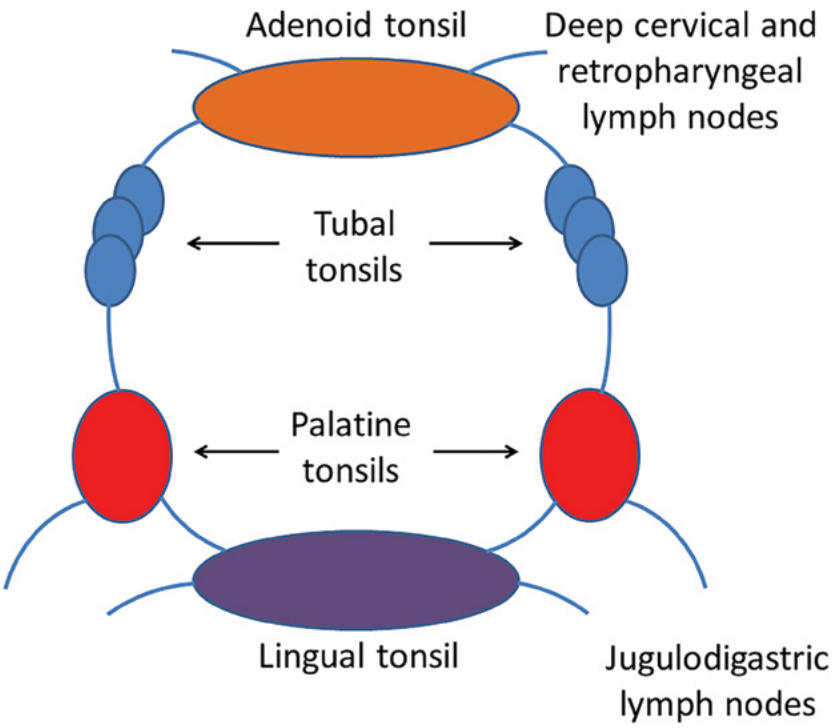

Figure 1 The 4 areas of tonsil tissue: the paired palatine tonsils (at both sides in the back of the mouth), the nasopharyngeal or adenoid tonsil (attached to the roof of the pharynx), the paired tubal tonsils (at the openings of the Eustachian tubes), and the lingual tonsil (located at the back of the tongue).

DISTINCT REGULATION OF TONSILLAR IMMUNE RESPONSE IN RESPIRATORY VIRAL INFECTIONS

Susceptibility to certain viral infections and defects in viral clearance could play a role in pulmonary inflammatory processes. Deficient innate and adaptive immune responses contribute to the morbidity and mortality of viral infections. Tonsillar cytokine expression is closely related to existing viral infections, age and allergic diseases and show distinct clusters between anti-viral and immune regulatory genes (Figure 3).

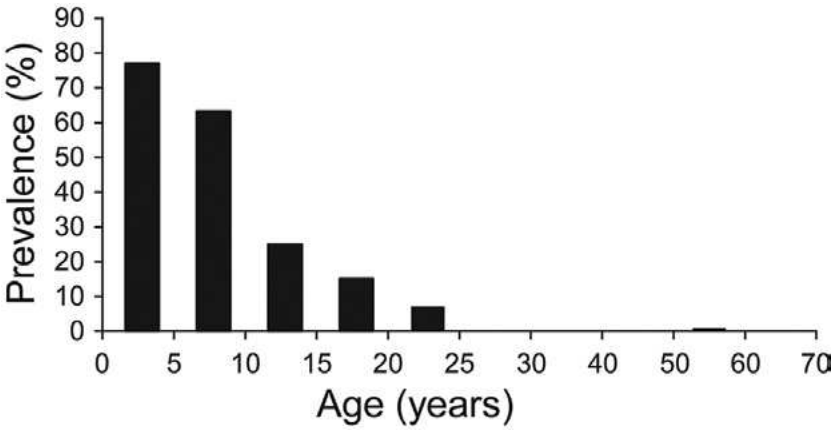

Figure 2 Age-dependent decrease in intratonsillar virus detections. (*Adapted from Jartti T, Palomares O, Waris M, et al. Distinct regulation of tonsillar immune response in virus infection. Allergy 2014;69:658-667.*)

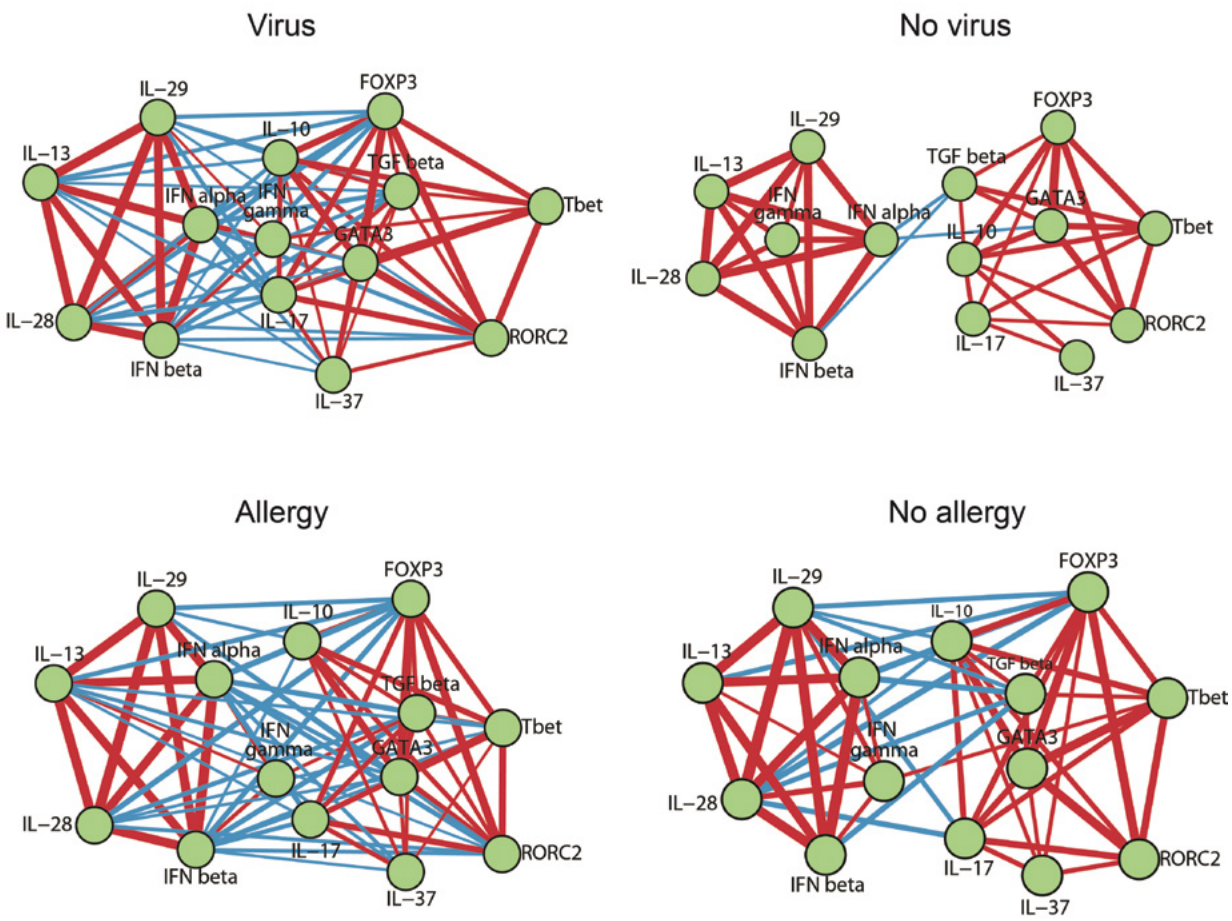

Figure 3 Age-dependent adjusted network representation of the significant intratonsillar gene correlations according to intratonsillar virus infection and allergic status. Nodes indicate genes. Lines indicate presence of significant correlations. Positive correlations are displayed as red and negative correlations as blue. The line thickness is proportional to the magnitude of the correlation coefficient. (*Adapted from Jartti T, Palomares O, Waris M, et al. Distinct regulation of tonsillar immune response in virus infection. Allergy 2014;69:658-667.*)

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9 EOSINOPHILS IN ALLERGIC RHINITIS

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KEY MESSAGES

- allergen-specific IgE and eosinophilic inflammation are key features that distinguish allergic rhinitis (AR) from other forms of rhinitis
- the presence of eosinophilia in the nasal mucosa of AR patients has been long established and has been related to disease severity and to the occurrence of co-morbidities such as nasal polyps and chronic rhino-sinusitis
- exposure to allergen increases nasal eosinophilia, while steroids and allergen immunotherapy significantly diminishes it

Allergic rhinitis (AR), or allergic inflammation of the nasal airways, is the most prevalent chronic non-communicable disease, affecting 10–25% of people annually. The characteristic symptoms of AR are rhinorrhea (excess nasal secretion), itching, sneezing, nasal congestion and obstruction. The immune response in AR is initiated by T cell production of Th2 cytokines, which drive IgE cross-linking on surface of mast cells resulting in release of preformed mediators such as histamine, leukotrienes and prostaglandins (early response). This is followed by recruitment of inflammatory cells, namely eosinophils and CD4+ T cells to the nose resulting in nasal edema and obstruction (late phase). The key features of AR (which distinguish AR from other forms of rhinitis such as non-allergic rhinosinusitis) include allergen-specific IgE and eosinophilic inflammation.

The presence of eosinophilia in the nasal mucosa of AR patients has been long established (Figure 1A). Nasal allergen provocation in AR patients leads to increase in tissue eosinophilia (Figure 1C and D), as well as expression of pro-eosinophilic cytokines such as IL-5 and GM-CSF. Following allergen challenge, there is a local increase of eosinophil precursors and progenitors in the nasal tissue as well as local eosinophil differentiation. In seasonal AR, there is an accumulation of activated eosinophils during natural grass-pollen exposure. Eosinophil counts as well as eosinophil cationic protein (ECP) in nasal secretions were related to the severity of symptoms in seasonal AR and can be used for the diagnosis and management of AR.

Chronic and/or untreated AR may result in complications which include recurrent chronic sinusitis and formation of nasal polyps. There is a large accumulation of eosinophils and their cytokines in both of these cases. These effects can be largely attributed to IL-5 and eotaxin (Figure 2), an eosinophil chemo-attractant, whose production is significantly increased in the nasal mucosa, although others including GM-CSF and RANTES are likely to contribute.

In grass-sensitive patients, allergen immunotherapy effectively inhibits allergen-induced infiltration of eosinophilia. Steroids effectively reduce activated eosinophils in seasonal AR (Figure 1B), in patients with nasal polyps or with severe chronic sinusitis. Together these data suggest that eosinophil is a critical cell involved in the pathogenesis of AR.

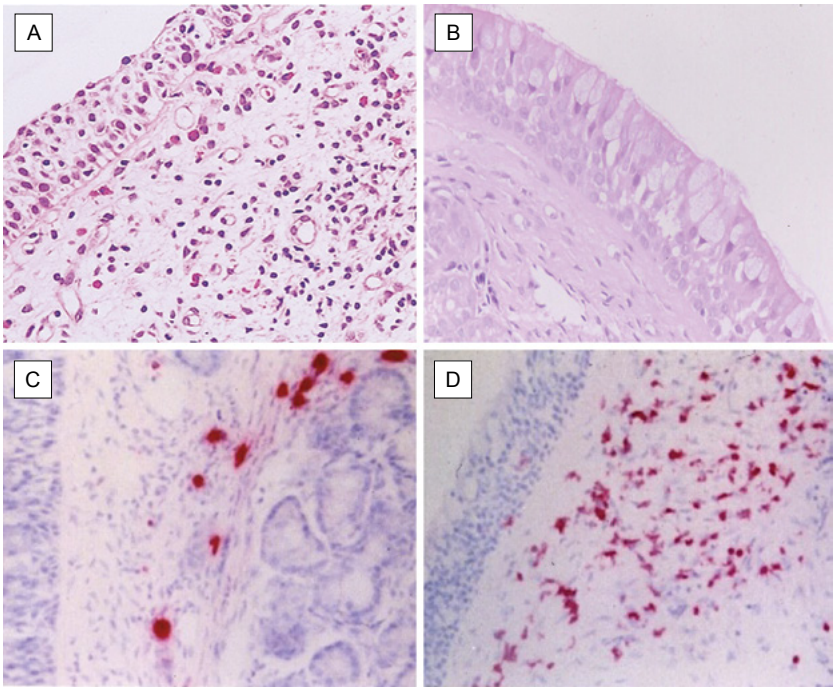

Figure 1 Increased eosinophil numbers in biopsies from patients with allergic rhinitis (A) is inhibited with use of steroids (B). Increased presence of eosinophils in the nasal inferior turbinate in allergic rhinitis (C) is further augmented after (D) allergen challenge.

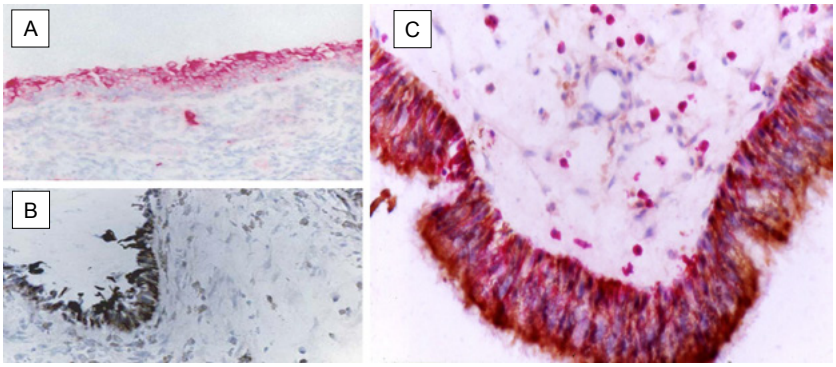

Figure 2 Eotaxin immunoreactivity (A) and mRNA (B) (*in situ* hybridization) in the nasal mucosa of a patient with allergic rhinitis (A). Eotaxin co-localises with cytokeratin (C) in the nasal epithelium as well as with local inflammatory cells.

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10 ANTIGEN PRESENTING CELLS IN ALLERGIC RHINITIS

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KEY MESSAGES

- Antigen-presenting cells act at the interface of innate and adaptive immunity and are crucial in determining whether allergic sensitization or tolerance develops
- The most important antigen-presenting cells the in nasal mucosa in allergic rhinitis are myeloid and plasmacytoid dendritic cells and Langerhans cells
- Dendritic cells process the allergen into small peptides that are presented onto MHCI and MHCII to T cells
- Dendritic cells can induce, maintain and propagate allergic inflammation and represent relevant therapeutic targets

The processing and presentation of allergens by antigen-presenting cells (APC) to T-lymphocytes is a prerequisite for allergic sensitization and thus for the allergic reaction per se. However such a reaction will develop, only under specific conditions, while the normal response that is induced is immune tolerance to allergens. The type and amount of allergen as well as the context in which APCs come into contact with antigens is crucial for the final fate of the immunologic reaction toward the antigen.

A number of different cell types are capable of acting as APCs, but the most important and effective are dendritic cells (DC). Mainly, three different types of dendritic cells are present in the human nasal mucosa: CD11c+ myeloid DCs (mDCs) and CD123+ plasmacytoid DCs (pDCs), and Langerhans cells (CD1a+, CD207+) that have different properties and ontogeny. In the human nasal mucosa, dendritic cells have first been described by Haas, and Langerhans cells by Fokkens. Recent literature has furthermore demonstrated that mDCs and pDCs are both present in the mucosa of allergic rhinitis (AR) patients and that their reaction after allergen contact might promote inflammation.

DCs process the allergen into small peptides that are presented onto MHCI and MHCII to T cells. They act at the interface of innate and adaptive immunity and can set the course toward a Th2-type allergic reaction or - under different circumstances - toward Th1-, Th17-, or T regulatory reactions. Generally, antigen presentation by pDCs will lead to tolerance while engagement of mature DCs will promote allergic reactions. Important determinants for the type of immunologic reaction are the cytokine milieu at the site, the time of contact and the concurrent exposure to adjuvants, such as diesel exhaust particles or enzymatically active allergen components.

Apart from their essential role in the pathogenesis of allergic reactions, dendritic cells have also been demonstrated to be relevant in the maintenance and propagation of allergic inflammation and thus in the development of clinical symptoms.

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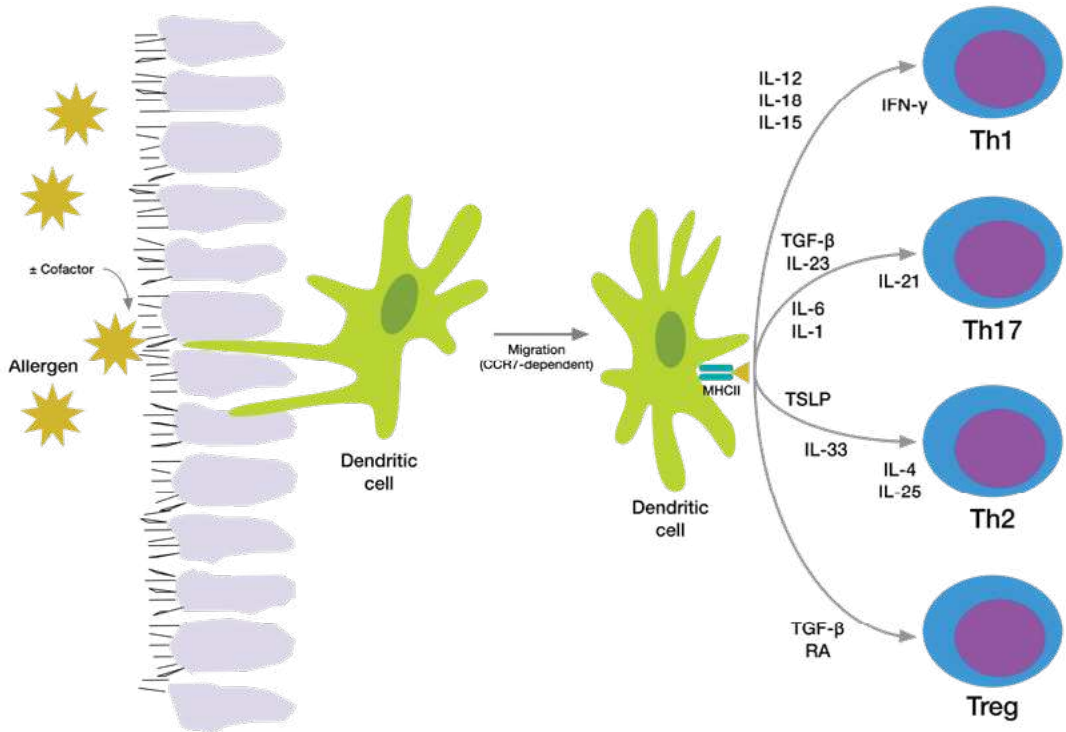

Figure 1 Dendritic cells (DC) control the type of the T-cell response. DCs collect allergens at the epithelium, process the allergen into peptide fragments and migrate to lymphoid tissue. DCs present the peptides onto MHCII to CD4+ lymphocytes. Dependent on the cytokine milieu T-cells differentiate to different phenotypes.

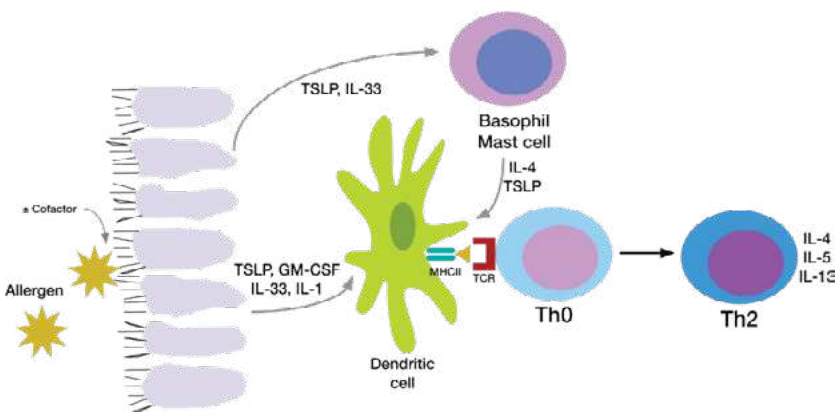

Figure 2 Interaction between epithelium, dendritic cells and T-lymphocytes. Cofactors and protease components of allergen activate the innate receptors on the epithelium leading to cytokine release (TSLP, IL-33, GM-CSF, IL-1) by epithelial cells. These cytokines activate DCs, induce recruitment of basophils, mast cells, and Th2 cells who also contribute to a cytokine milieu that favors the differentiation of naïve T-cells into Th2-lymphocytes.

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11 THE ROLE OF T- AND B-LYMPHOCYTES IN ALLERGIC DISEASE

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KEY MESSAGES

- Allergic disease is a case of mistaken identity, where a parasitic T and B cell response is triggered against harmless environmental molecules
- In allergic disease not only eosinophils of prototypical Th2 responses are recruited, but also neutrophils of the Th17 type and macrophages of the Th1 type play roles
- Plasticity of pro-inflammatory and regulatory T and B cells adds a new layer of complexity to the immune response
- Understanding regulatory networks that control T and B cell differentiation could potentially identify molecular targets for intervention

The general role of T and B lymphocytes in the adaptive immune response is well established (Figure 1). Depending on the specific microbiological threat the immune system encounters a dedicated subclass of CD4 T helper cells is induced by the interaction and activation of dendritic cells. These T helper cells in turn may induce and activate effector cells such as eosinophils or neutrophils, or may activate B cells to become plasma cells that produce pathogen specific immunoglobulins.

In the case of allergy, harmless environmental molecules like grass or tree pollen, animal dander, or house dust mite droppings are mistaken for parasites and the immune system elicits a strong Th2 and IgE-driven response that fails to remove these "irrelevant threats" yet does induce the clinical symptoms of rhinorrhoea, nasal congestion, and itching. Another specific class of T cells, the regulatory T cells (Tregs) is able to dampen immune responses. Distinct subclasses of Tregs can be discerned that differ in their origin (naturally occurring and produced in the thymus or induced in the periphery) and/or expression of the differentiation markers Foxp3 and CD25, or the expression of the effector cytokines IL-10 and TGF-beta. Just like the expression of effector cytokines define and mediate the downstream effects of T helper cells, the induced or constitutive expression of IL-10 and TGF-beta by Tregs inhibits the activation of other T-, B-, and dendritic cells, or the antigen driven activation of mast cells. In the case of Foxp3-CD25 positive Tregs that do not produce IL-10 or TGF-beta, a direct physical interaction with other T cells blocks the T cell receptor mediated activation. Interestingly, these Tregs have been shown to be part of the mechanism by which allergen immunotherapy suppresses symptoms.

T and B cells have been used in many *in vivo*, *in vitro*, or animal model systems to study specific diseases like allergy. Current interests try to link specific genomic mutations (SNPs), expression profiles, or epigenetic changes in T and B cells to the risk of individuals to develop allergy or to study the regulatory network that controls the activity and functionality of these cells.

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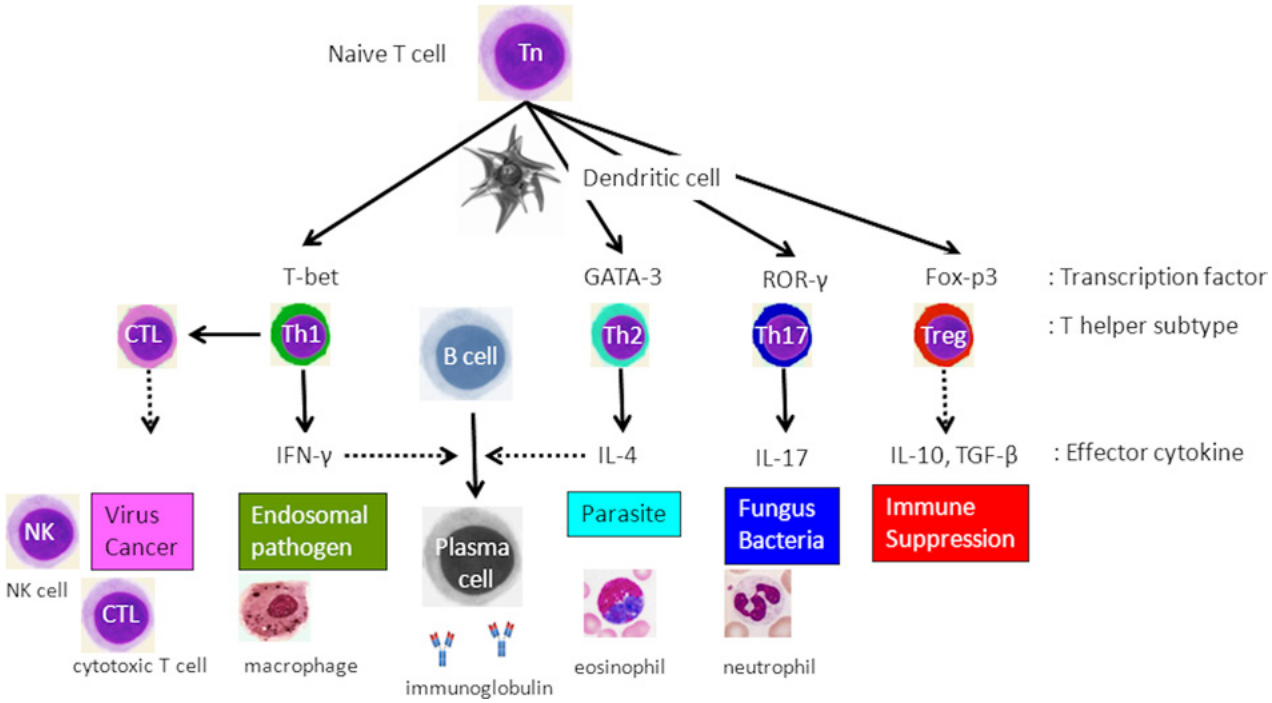

Figure 1 Overview of T and B cells differentiation in relation to potential microbiological threats.

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12 CYTOKINES AND CHEMOKINES IN ALLERGIC RHINITIS

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KEY MESSAGES

- Cytokines ensure communication between the immune system cells and with other cells of the body and act as a network governing the elicitation, amplification and resolution of inflammation
- Several subtypes of cytokines are described according to their main biological effect: sensing cytokines, T-cell instructing cytokines, effector cytokines and resolving cytokines
- Chemokines create a gradient (chemotaxis) that decides which type of inflammatory cells and which type of T and B cells are recruited in the nasal mucosa in allergic rhinitis

Cytokines are soluble proteins or peptides that act as the hormones - messengers - of the immune system. They confer cell-to-cell communication, which may take place between adjacent cells (**juxtacrine**) or cells in different organs of the body (**para- or endocrine**). A cytokine signal is delivered via a receptor on the surface of a cell, and since different cells may express the same receptor, a cytokine can have several functions (**pleiotropy**) depending on the target cell.

A special subgroup of cytokines is constituted of the so-called chemokines that attract leukocytes to the site of inflammation, and the immune system uses these to move leukocytes in the tissues, when they have left the bloodstream. The chemokines are key players in attracting the leukocytes to inflamed areas such as the nose in allergic rhinitis (AR). The chemokines have a fairly similar biochemical structure, and are divided according to the placement of two intramolecular cystin-bridges (Figure 1) into groups: CC, CXC or CX3C, where X denotes a non-cystein amino acid residue.

Various groups of cytokines are responsible for the different phases of the allergic **sensitization** (building up the allergic immune response) and **elicitation** (reactions upon exposure to an allergen):

The sensing cytokines (Figure 2, yellow), IL-33, IL-25 and TSLP are released from the epithelial cells of the nasal mucosa and signal to the allergen-presenting dendritic cells to take up incoming allergens and bring them to the lymph nodes.

The T-cell instructing cytokines (Figure 2, green) will instruct undifferentiated T-helper (CD4+) cells to develop into different kinds of cells, each of them equipped for different kinds of immune response: IL-12 and γ-interferon will produce type 1 T-helper cells (Th1) that helps fighting bacteria and virus, IL-4 leads to Th2 cells which fights large multicellular parasites like worms, but unfortunately also create the allergic immune response. Other Th-cell types such as Th17 (believed to be active in fighting bacterial fungal infections, but unfortunately also involved in autoimmune diseases), and Tregulatory (dampening the inflammation) also exists.

T-cell effector cytokines (Figure 2, red) are the cytokines by which T helper cells exerts their action: Th2 cells release IL-4 and IL-13, which instructs B-cells to produce the allergy antibody IgE, IL-5 that causes the bone marrow to form the eosinophilic granulocyte, and IL-9 that together with IL-13 creates the allergic inflammation e.g. in the nose as is the case in allergic rhinitis.

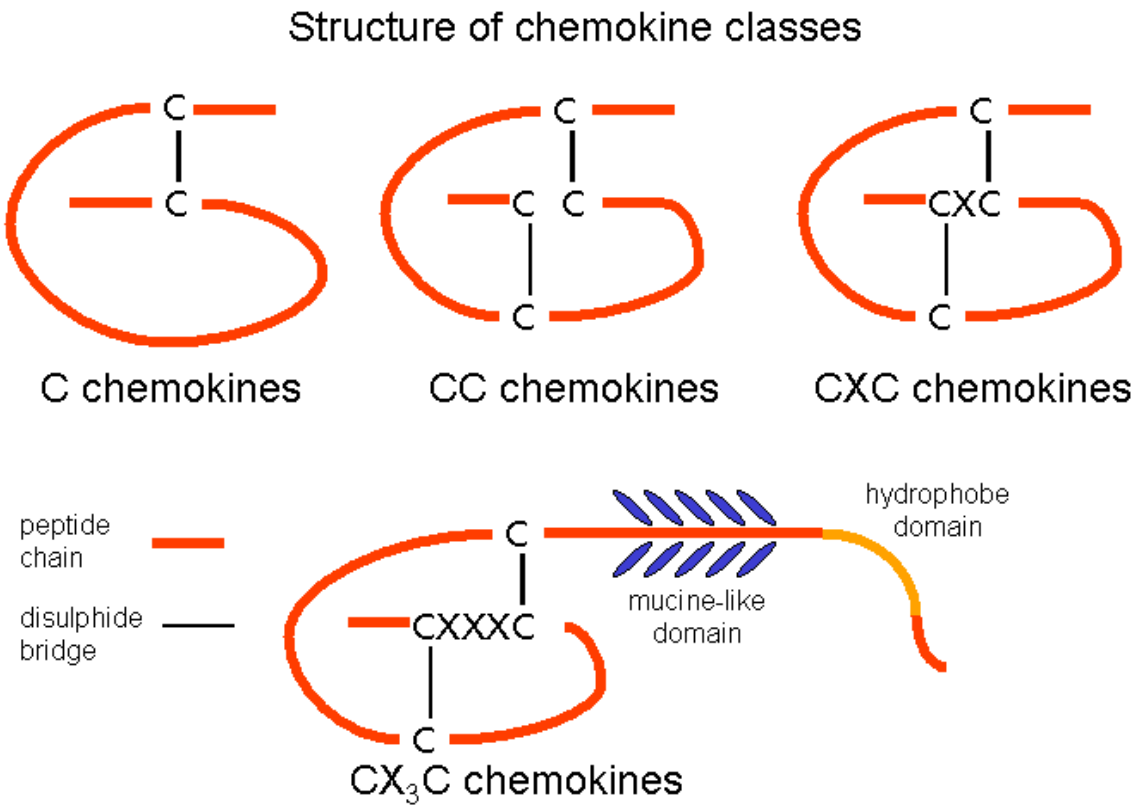

Figure 1 Chemokine classes according to their structure. (*Copyright Kohidai, L.*)

Chemokines (Figure 2, purple). When chemokines are secreted from inflammatory cells, a gradient builds up, where the highest concentration is closest to the secreting cell, and in this way different leukocytes may sense instructions about direction. The movement of cells up against a gradient is called chemotaxis, and the large number of chemokines and their corresponding receptors, constitute an elaborate system, that can decide which inflammatory leukocytes, e.g. eosinophils, neutrophils, basophils or T- and B-cell subpopulations are attracted to a certain site in the nasal mucosa. It is likely that the organ in which the allergic reaction takes place: the nose, the lungs or the skin make use of different chemokines, thus also transferring organ specificity to the inflammatory response. Some chemokines may also - at higher concentrations - activate leukocytes to release mediators, and in this way they become important the important directing players in the allergic reaction. The most important chemokines in the allergic inflammation are eotaxin-1 (CCL11), eotaxin -2 (CCL24) and eotaxin -3 (CCL26) all of which act via the CCR3-receptor present on eosinophils, basophils and certain T helper-cell populations. Another, more generally acting Th2 chemokine, is RANTES (CCL5) that acts via the CCR5-receptor.

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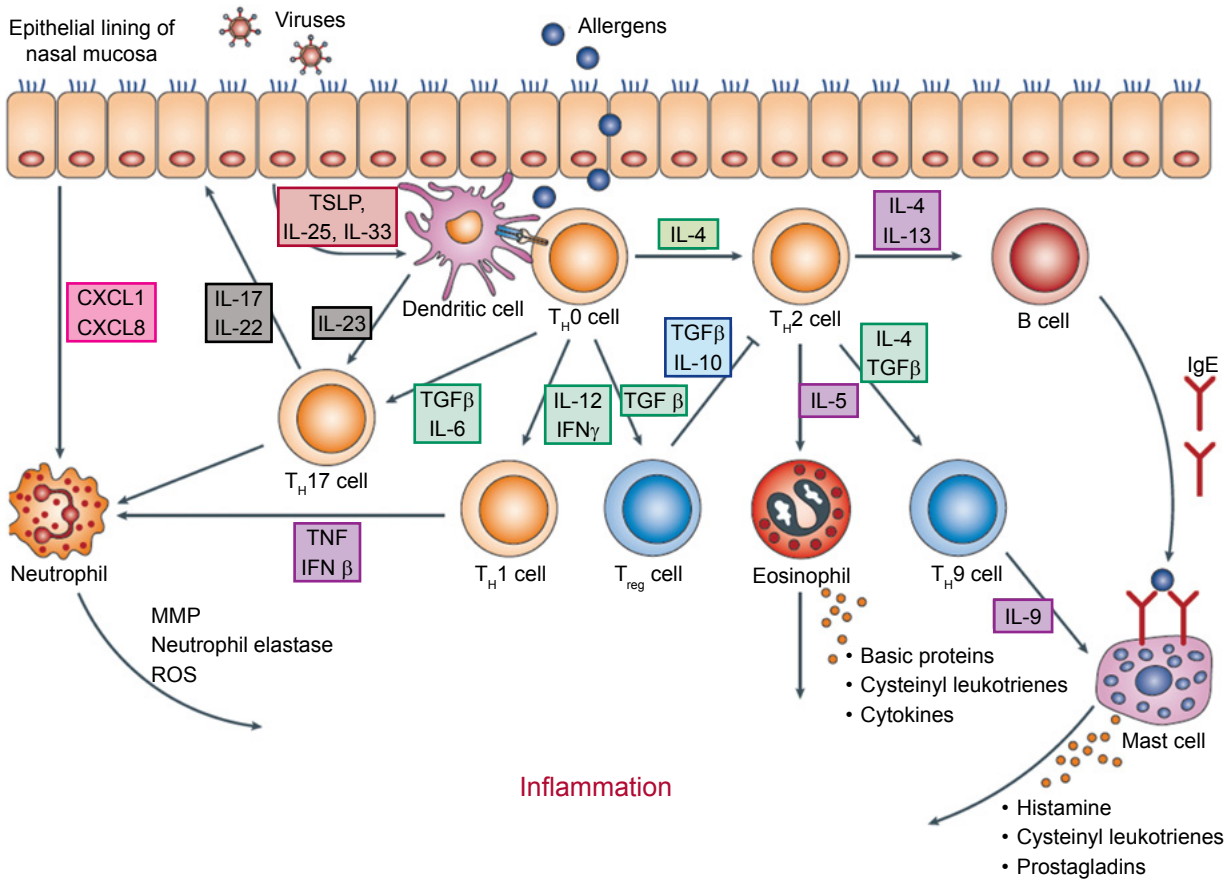

Figure 2 The complex interplay of cytokines and chemokines inducing, augmenting or resolving inflammation in the nasal mucosa in allergic rhinitis

13 LOCAL AND SYSTEMIC IgE IN ALLERGIC RHINITIS

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KEY MESSAGES

- Local production of IgE in target organs may explain why some patients develop rhinitis, others asthma or eczema alone or in combination. Conversely the absence of local IgE may explain why up to 50% of the population who demonstrate positive skin tests/IgE have no clinical manifestations of allergy
- In a minority of patients, typical symptoms of allergic rhinitis (AR) are described, but systemic IgE and skin prick tests are uninformative. These patients previously labelled as having 'non allergic' or 'idiopathic' rhinitis may potentially have a local IgE-dependent rhinitis
- Local IgE synthesis in AR was suggested by the detection of interleukin 4 and epsilon gene transcripts by *in situ* hybridization in B cells in the nasal mucosa and confirmed in supernatants of nasal biopsies cultured *in vitro* with IL-4 and CD40 ligand

The diagnosis of allergic rhinitis (AR) depends upon symptoms of nasal itching/sneezing, watery discharge and congestion following relevant aeroallergen exposure accompanied by objective evidence of IgE sensitivity **commensurate with the history**. However, there is a minority of patients, who describe typical symptoms of AR in whom systemic IgE is undetectable and skin prick tests are negative.

Huggins and Brostoff were the first to demonstrate this phenomenon by positive nasal provocation tests with house dust mite extract in patients with perennial symptoms on dust exposure but negative skin tests/serum IgE concentrations. Subsequently, local IgE synthesis in AR was suggested by the detection of interleukin 4 and epsilon gene transcripts by *in situ* hybridization in B cells in the nasal mucosa (Figure 1). **Local** IgE protein production was confirmed in supernatants of nasal biopsies cultured *in vitro* with IL-4 and CD40 ligand. Actual heavy chain gene switch recombination occurring locally, rather than as a consequence of recruitment of already-switched B cells, was strongly supported by the detection of local heavy chain DNA switch circles and activation-induced cytidine deaminase (AID) RNA necessary for local switch recombination to occur.

Whereas allergy is regarded as a systemic disease, the local production of IgE in target organs may explain why some patients get rhinitis, others asthma or eczema alone or in combination. Conversely the absence of local IgE may explain why up to 50% of the population, who demonstrate positive skin tests/IgE have no clinical manifestations of allergy, although this remains to be tested. Patients previously labelled as having 'non allergic' or 'idiopathic' rhinitis may potentially also have a local IgE-dependent rhinitis.

In an elegant series of studies Rondon, Blanca and colleagues have characterised such 'local allergic rhinitis' (LAR) in a Spanish population. The allergens responsible include house dust mite, grass pollen and olive pollen. In such patients, serum specific IgE and skin tests are uninformative and nasal provocation testing with the relevant allergen(s) is needed. In addition to early and late phase symptoms, nasal allergen provo-

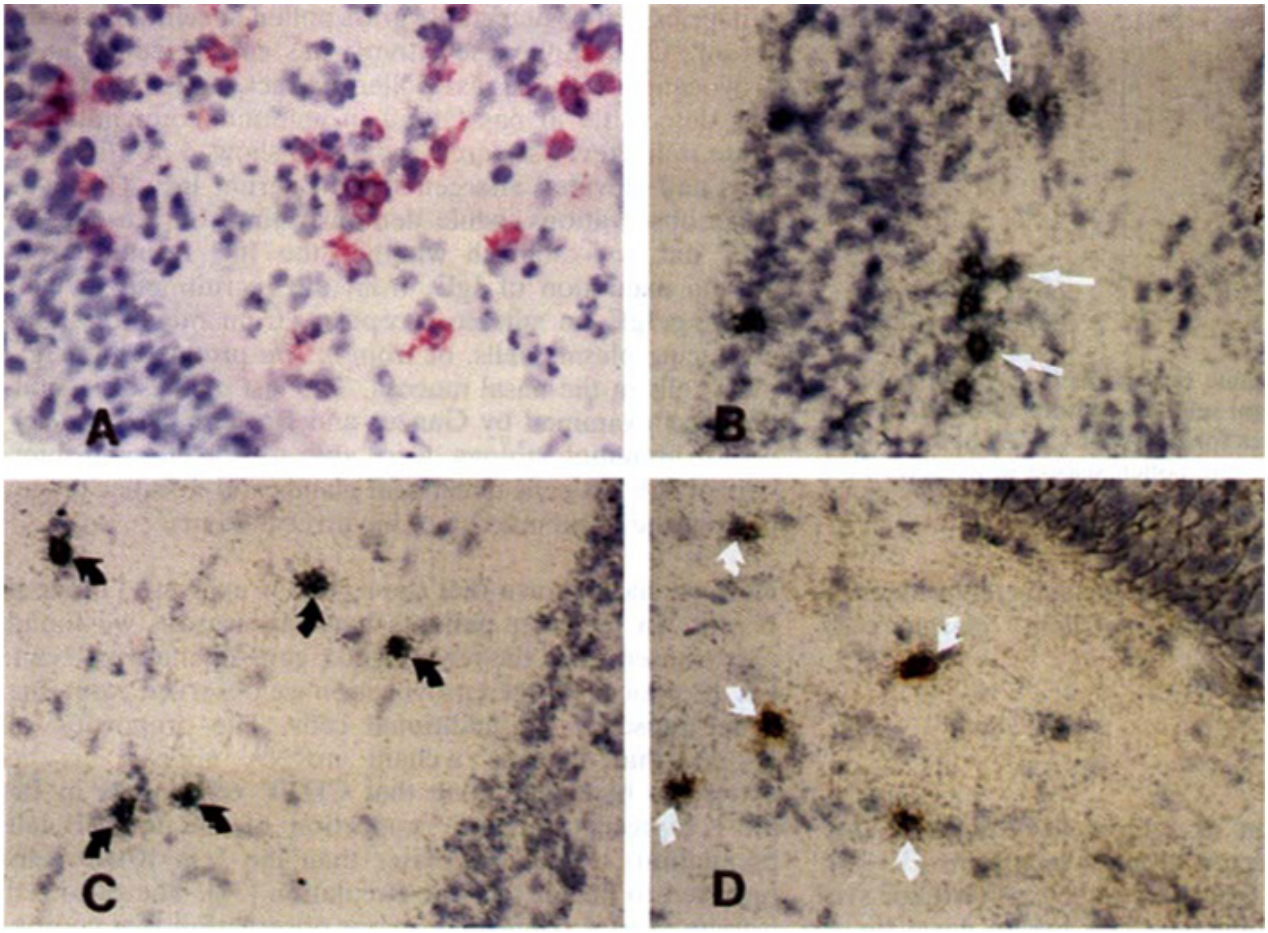

Figure 1 Immunohistology and in situ hybridization of nasal biopsy specimens. (A) CD20' B cells, (B) IL-4 mRNA+ cells, (C) IgE Cε+ cells after allergen challenge, which are colocalized to CD20+ cells, (D) by use of double immunohistochemistry/in situ hybridization. (*Reproduced from Durham SR, Gould HJ, Thienes CP, et al.,Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. Eur J Immunol 1997;27: 2899-2906, with permission from Wiley-Blackwell.*)

cation in LAR resulted in immediate tryptase release and a more delayed release of eosinophil cationic protein and Th2 cytokines in nasal lavage. Somewhat surprisingly they were able to detect local IgE in nasal lavage in only a proportion of subjects although attributed this to low IgE concentrations and to the effects of dilution by nasal lavage.

Outstanding issues include the need to establish the prevalence of LAR in different countries, the natural history of LAR and whether LAR may respond to usual nasal therapies including allergen immunotherapy – possibly delivered by the nasal route? Nasal provocation tests require standardisation with careful consideration of relevant threshold allergen concentrations. Meanwhile the mainstay of diagnosis of AR remains a careful history with skin tests and/or serum specific IgE, whereas nasal provocation has assumed an increasingly important role, not only for research, but also for use in patients with a clear-cut history in whom conventional IgE tests are negative (Figure 2).

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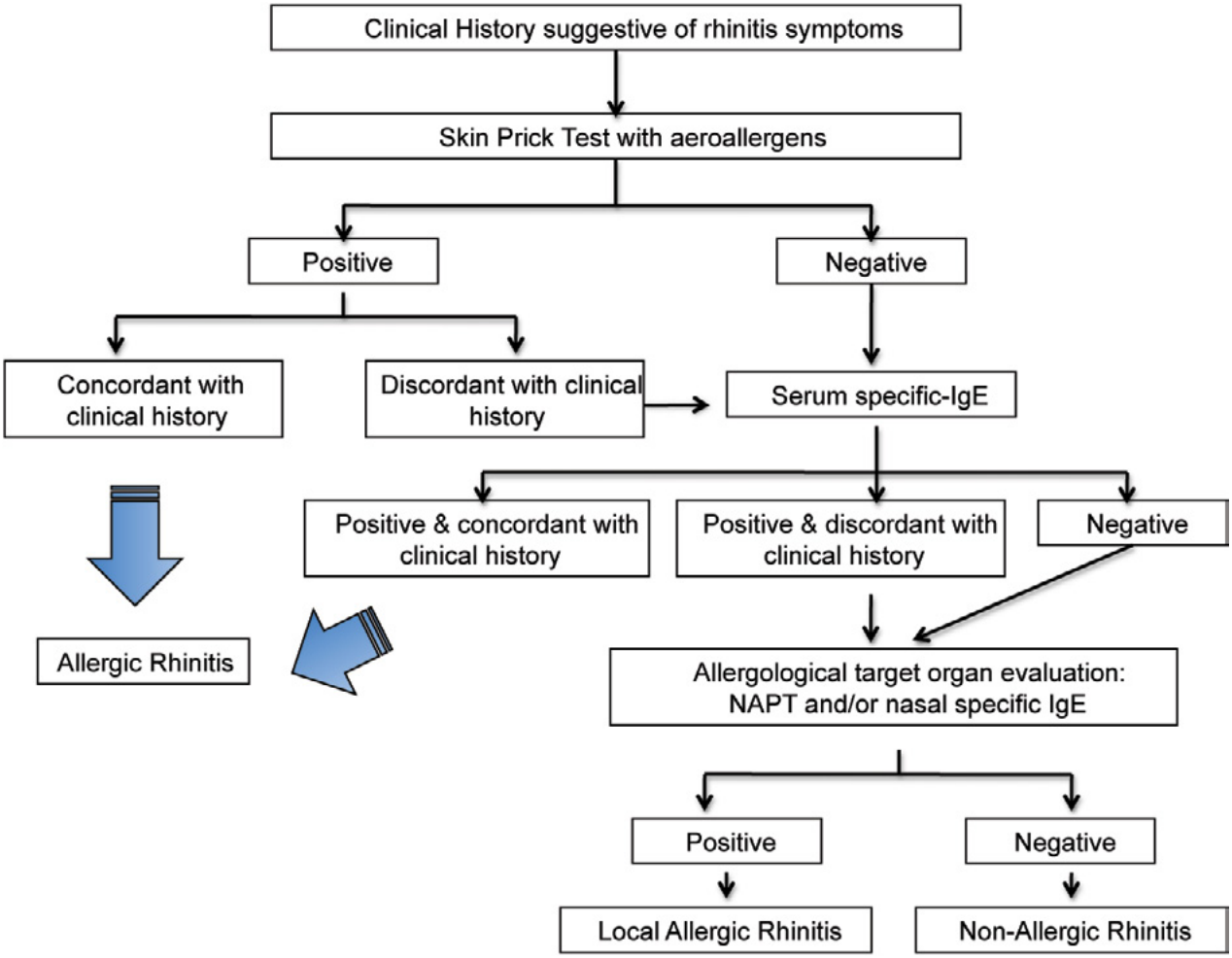

Figure 2 Diagnostic approach in patients with local allergic rhinitis (LAR). (*Reprinted from J Allergy Clin Immunol, 129/6, Rondón C, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, Mullol J, Blanca M. Local allergic rhinitis: concept, pathophysiology, and management, 1460-1467, Copyright 2012, with permission from Elsevier.*)

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14 IgE REPERTOIRES IN ALLERGIC RHINITIS

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KEY MESSAGES

- Humans have the potential to produce at least 10^{11} antibody specificities with five antibody classes that perform different functions
- Antibody (immunoglobulin) genes may undergo somatic hypermutation, class switch recombination and affinity maturation to generate diversity in the B cell or antibody repertoire
- In sensitised individuals, IgE antibodies enable a rapid and potent immune response (immediate hypersensitivity) to allergens; in allergic rhinitis (AR) this response takes place at the initial site of allergen exposure in the nasal mucosa
- Next generation sequencing of expressed immunoglobulin genes in AR has revealed the clonal amplification, diversification and selection of IgE-expressing B cells in the nasal mucosa

B cells are generated in the bone marrow, where they acquire 'recombinatorial diversity' by the random recombination of immunoglobulin gene fragments and 'junctional diversity' by the deletion or addition of nucleotides at recombination junctions (Figure 1). Upon activation by antigen, mature cells may be further modified by somatic hypermutation (SHM) during affinity maturation. Competition for antigen results in selective survival and proliferation of high affinity clones. In parallel, the cells undergo class switch recombination (CSR) from IgM to IgG, IgA or IgE (direct switching). IgG- and IgA- expressing B cells can also switch to IgE (sequential switching) and this may be the predominant pathway for local IgE production in allergic rhinitis (AR). Sequential switching is correlated with affinity maturation in IgE.

Every B cell clone expresses a unique immunoglobulin. Diversification of a B cell clone during an immune response generates clonally related progeny. Clones are associated with a hierarchy of mutations derived from the original immunoglobulin sequence assembled in the bone marrow. The entire population of B cells in an individual is termed the B cell repertoire. Until recently, analysis of the antibody repertoire was very labour intensive and limited to tens or hundreds of antibody sequences. This science has been revolutionized by the "next generation sequencing" (NGS) methods in which the sequences of millions of DNA molecules can be determined in parallel in a single experiment, approaching the complete repertoire of the B cell population in an individual. Pioneering studies of IgE repertoires by NGS in AR have provided valuable insights into the ontogeny of IgE-expressing cells. Analysis of matched blood and nasal biopsy samples in rhinitis patients demonstrated trafficking of B cells between blood and the nasal mucosa, supporting previous evidence that the nasal mucosa enhances the diversification of IgE-producing B cells (Figure 2).

In patients with AR, IgE repertoires have greater inter- and intra-clonal diversity and increased SHM compared to IgE from healthy controls (Figure 3). The level of SHM within the 'allergic' IgE repertoire was strongly influenced by seasonal exposure to allergen, particularly in local nasal tissue compared to the blood (Figure 4). The close

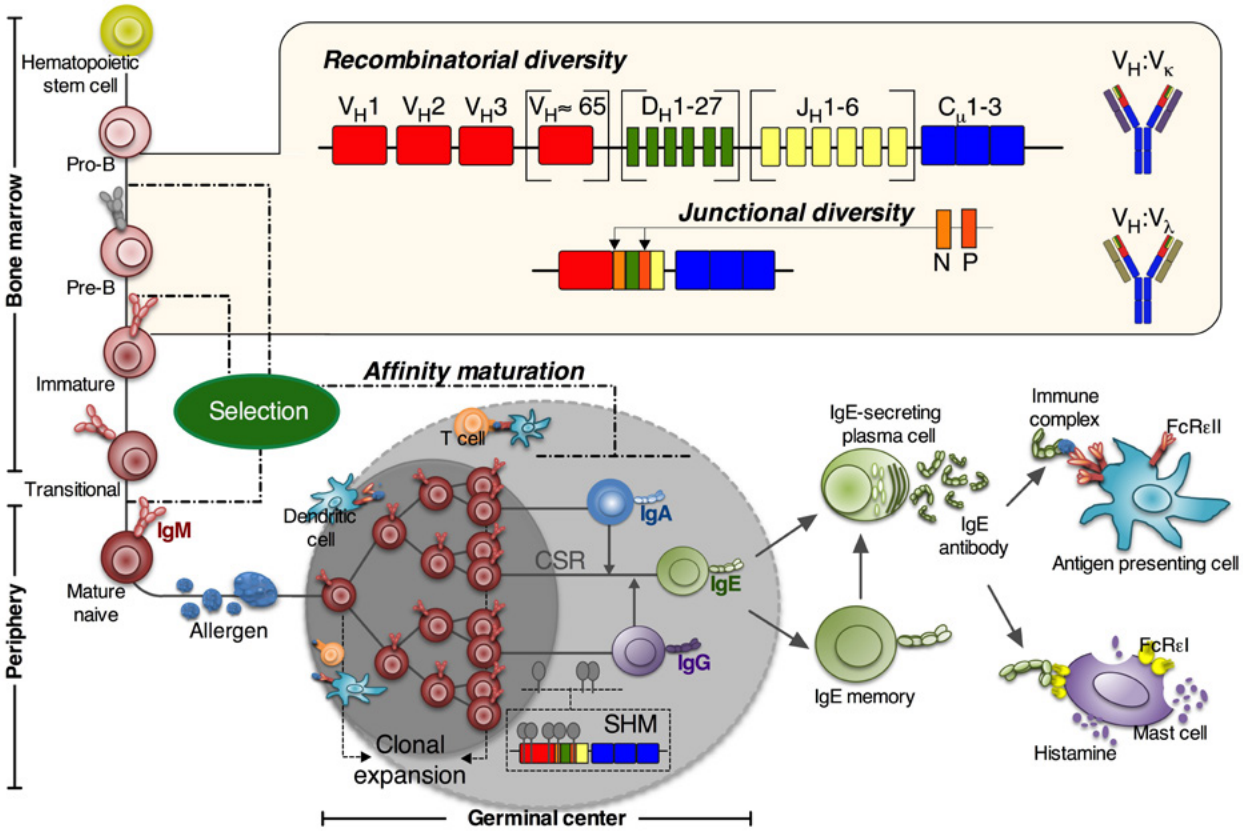

Figure 1 Diversity and selection of antibody repertoire. In the bone marrow, B cells acquire recombinatorial diversity by random shuffling of VDJ segments for the IgM (μ) heavy chain (V_H), and VJ for the kappa- (V_k) and lambda- (V_k) light-chains. Junctional diversity is simultaneously introduced by addition or deletion of nucleotides at breaks in the DNA before end-joining. Antigen exposure may induce SHM and CSR to IgE during affinity maturation of B cells in the germinal center of peripheral lymphoid tissue. In allergic patients, the production of IgE contributes to the allergic response by sensitising IgE effector cells and antigen-presenting cells for antigen-induced activation. Selection checkpoints are imposed to regulate clonal expansion and affinity maturation of B cells.

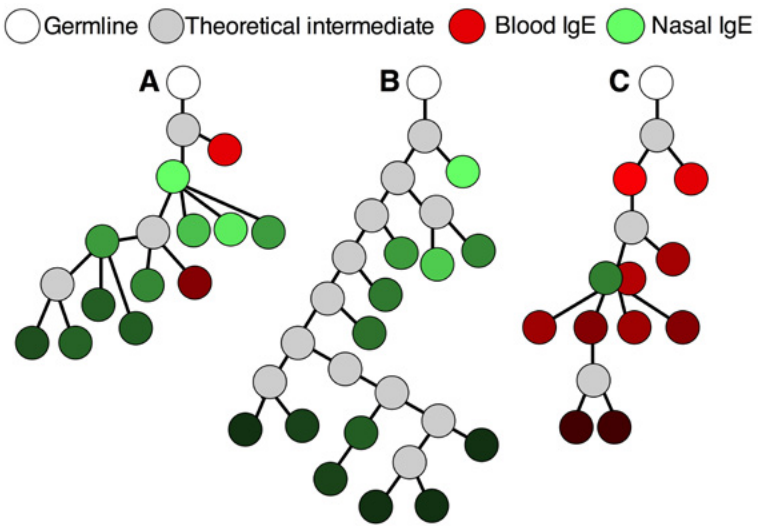

Figure 2 Formation of IgE lineage trees. IgE sequences that share a common ancestor are identified by alignment to germline sequences. Sequences that are more mutated are indicated by a darker shade. A & C highlight IgE clones that can be identified in both blood and nasal mucosa. B shows that IgE sequences can diversify within the nasal mucosal via SHM. Red circles indicate blood sequences, green circles indicate nasal sequences, open white circles indicate germline sequences and grey circles indicate theoretical intermediates that are not experimentally sampled.

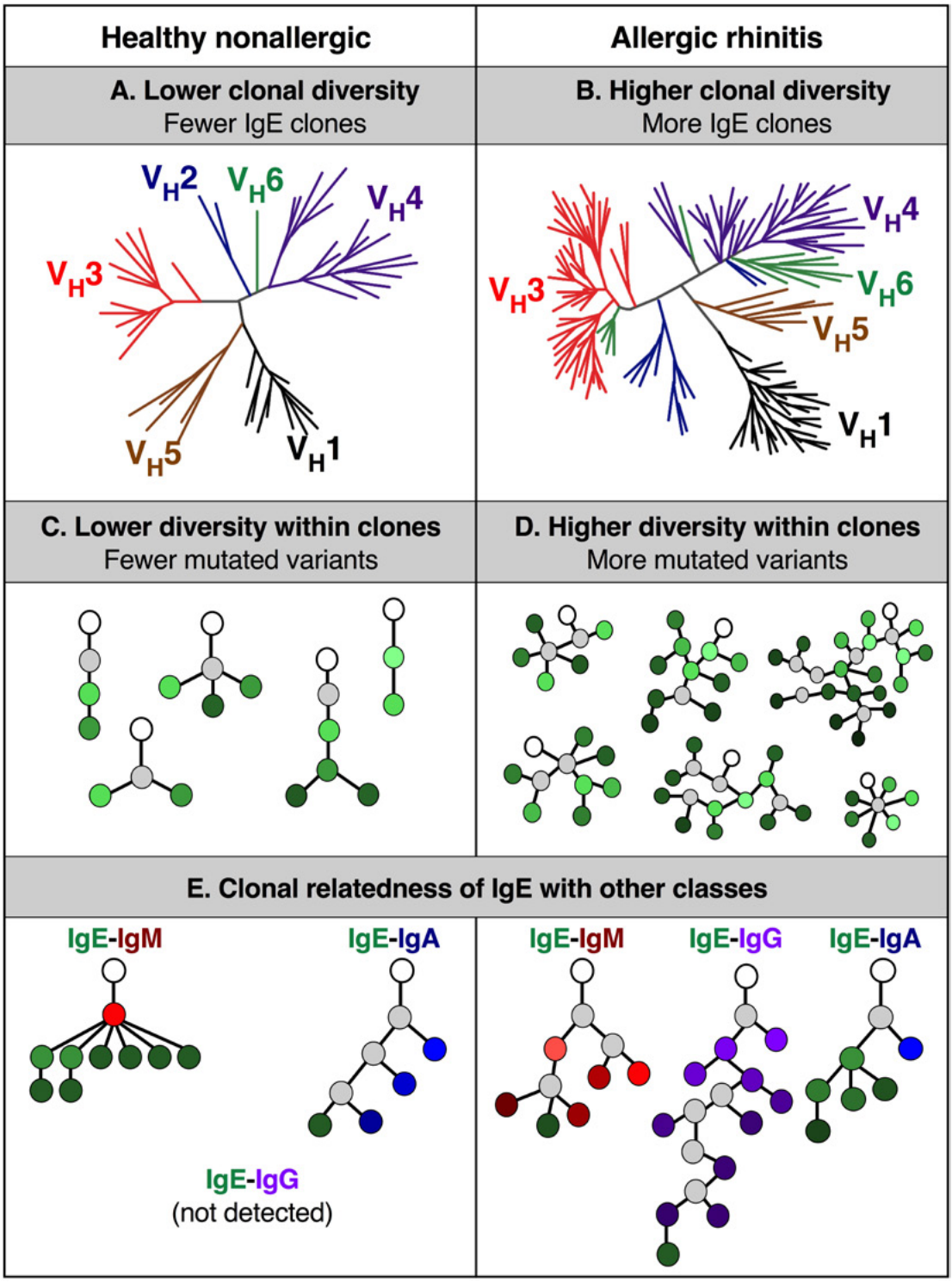

Figure 3 IgE repertoire differences between healthy controls (left column) and allergic rhinitis (right column). A & B: The IgE repertoire in AR encompasses a greater number of clones (*i.e.* more branches in the phylogenic tree) expressing different immunoglobulin genes (VH1-6) compared with healthy controls. C & D: IgE clones in AR contain more mutated family members as result of intra-clonal diversification. E: IgE sequences (green) share the same ancestors with IgM (red), IgA (blue) or IgG (purple) sequences in AR but only with IgM or IgA in healthy controls. C-E: Sequences with darker shades of colors are more mutated.

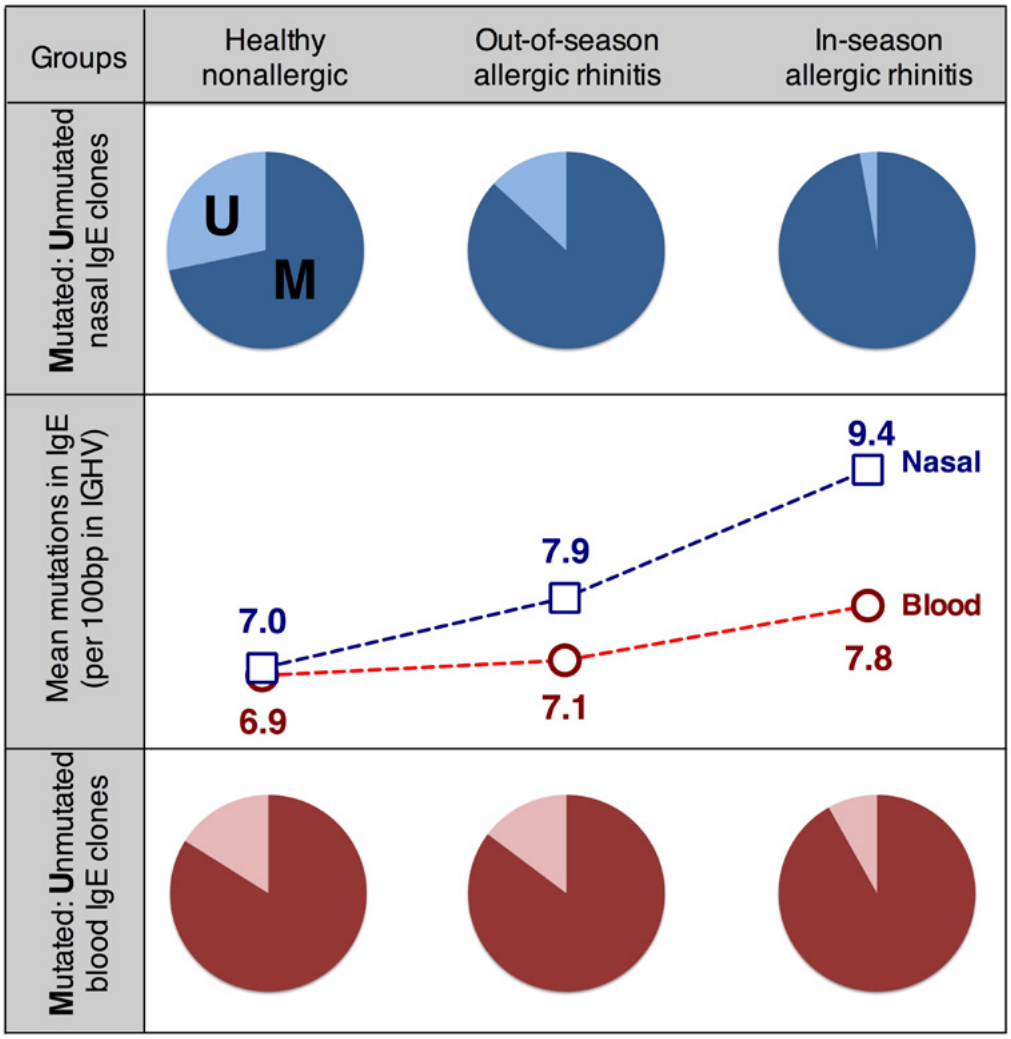

Figure 4 Increased mutation of IgE in response to seasonal allergen exposure. Seasonal pollen exposure increases SHM of IgE clones in the blood (red) and nasal mucosa (blue). The relative proportion of Mutated IgE versus Unmutated IgE clones was also altered in AR during the pollen season.

association between SHM and antibody affinity suggests that allergen exposure drives affinity maturation of B cells resulting in high affinity IgE that is central to the inflammatory allergic response. In contrast, in healthy individuals the IgE repertoire was less mutated.

Analysis of IgE repertoires in AR have provided valuable insights into the mechanisms of this disease and further support the concept that the nasal mucosa is an important source of local IgE.

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15 MicroRNAs IN ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- A variety of miRs are abnormally expressed in both allergic rhinitis (AR) and chronic rhinosinusitis (CRS)
- Inflammation and immune imbalance in AR and CRS may be promoted by miRs
- miRNAs have the potential to act as biomarkers of AR and CRS
- The miR expression profiles from different studies in AR have displayed a considerable discrepancy
- Functional pathways for miRs in AR and CRS need to be further studied

MicroRNAs (miRs) are evolutionally conserved small non-coding RNA molecules, only 18-22 nucleotides in length, which represent one of the fundamental epigenetic regulatory mechanisms used by cells. miRs are transcripted from genomic DNA and mature miRNAs are generated through multiple processes controlled by a set of enzymes (Figure 1). Mature miR is incorporated into the **RNA-Induced Silencing Complex** (RISC) and regulates gene expression by base pairing of the seed sequence to the 3'-UTR of target mRNA (Figure 1). Depending on the level of complementarity between miR and its target site, target mRNA degradation, translational repression, or both occur.

miRNAs are involved in diverse biologic processes including allergic responses. Several miRNAs have been found to target a number of immune genes such as IL-12p35, IL-13, IL-13Rα, **Cytotoxic T Lymphocyte–associated Antigen 4** (CTLA-4) and **Signal Transducer and Activator of Transcription-1** (STAT-1), as well as to modulate the function of various immune cells including T cells, dendritic cells, and macrophages which in turn affects the Th1/Th2 balance state (Figure 2).

miR IN RHINITIS AND RHINOSINUSITIS

Particularly in allergic rhinitis (AR), the miR profiles in nasal mucosa of AR patients have been explored. The results from different studies are inconsistent and the functions of most aberrantly expressed miRs remain undefined. MiR-224, miR-187, miR-143, and Let-7e have been reported to be down-regulated, whereas miR-155, miR-205, and miR-498 have been demonstrated to be up-regulated.

Cord blood IgE is associated with the development of aeroallergen sensitization. Decreased miR-21 expression in blood mononuclear cells has been associated with elevated IgE levels in cord blood and AR development. Since it is able to suppress **Transforming Growth Factor beta** (TGF-β) receptor 2 expression in monocytes, miR-21 has the potential to serve as early predictor of AR.

A variety of miR expression profiles have been found in patients with chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) in comparison with controls. miR-125b has been found up-regulated in eosinophilic CRSwNP. miR-125b is able to induce the production of type I interferon (IFN) via silencing human **eukaryotic Initiation Factor 4E** (eIF4E)-binding protein 1, which is a translational repressor of interferon regulatory factor

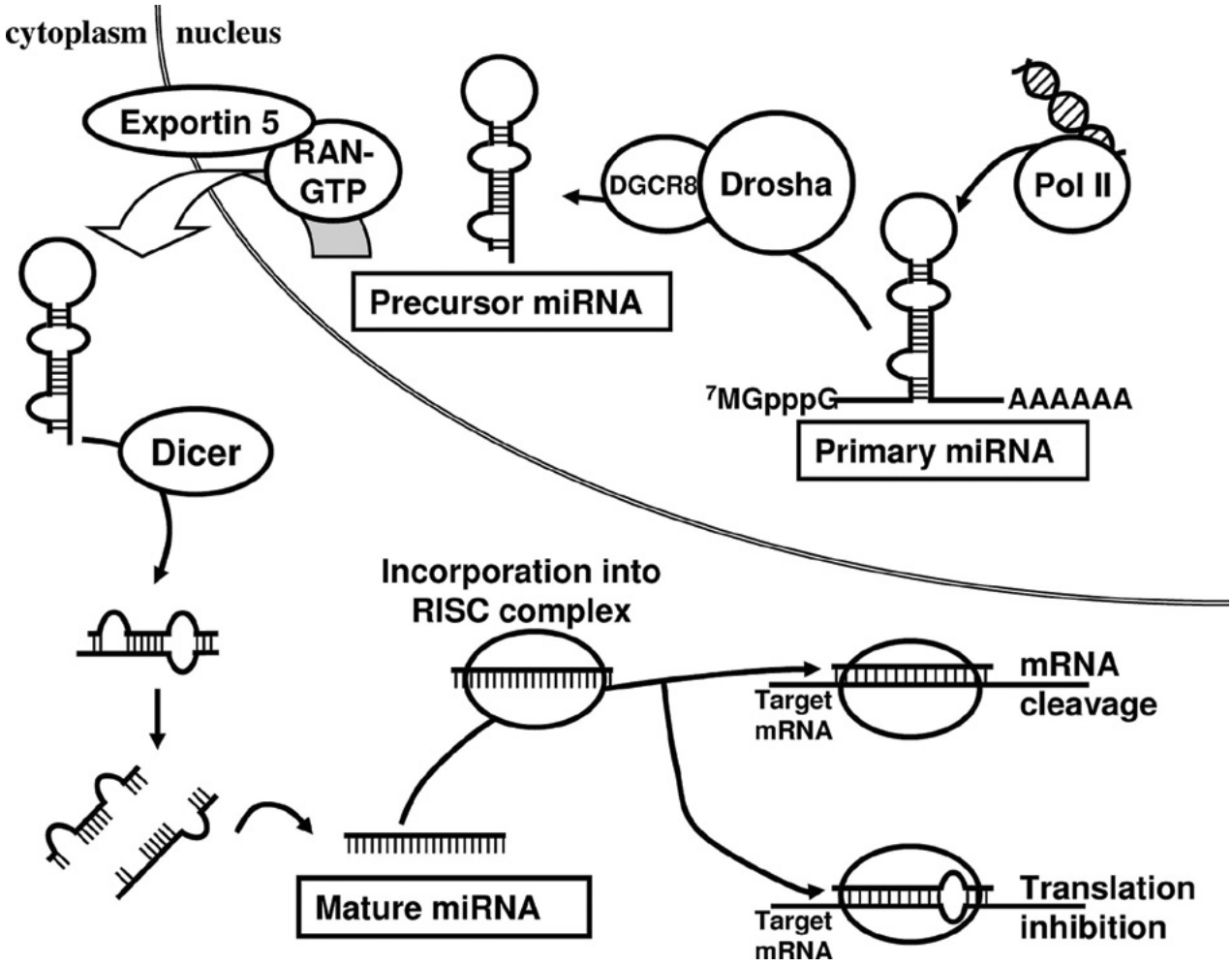

Figure 1 Biogenesis and mechanism of action of miRNAs. Primary miRs (pri-miRNAs) are transcribed by RNA polymerase II or III from specific genomic DNA and are processed by the RNase III endonuclease, Drosha, with its partner, DiGeorge syndrome critical region gene 8 (DGCR8), into 60-70-nucleotide hairpin miRNA precursors (pre-miRNAs) in the nucleus. The resulting pre-miRNAs are exported into the cytoplasm and then further processed by another RNase III enzyme, Dicer, into the mature miRNAs. One strand of mature miRNA duplex is assembled into the RNA-induced silencing complex (RISC). MiRNAs regulate gene expression by repressing translation or directing sequence-specific degradation of complementary mRNA. (*From: Chuang JC, Jones PA. Epigenetics and microRNAs. Pediatr Res 2007; 61: 24R-29R*).

7. Since type I IFN may promote mucosal eosinophilia in CRS, the overexpression of miR-125b may contribute to eosinophilic inflammation in nasal mucosa (Figure 3).

Overall, the research on miRNAs in AR and CRS is still in its early stages. The results from different studies are inconsistent, the functions of most miRs have not been well established, and the therapeutic effects of miRNAs in CRS and AR are still unknown. It remains as an unmet need to address these important challenges in future studies.

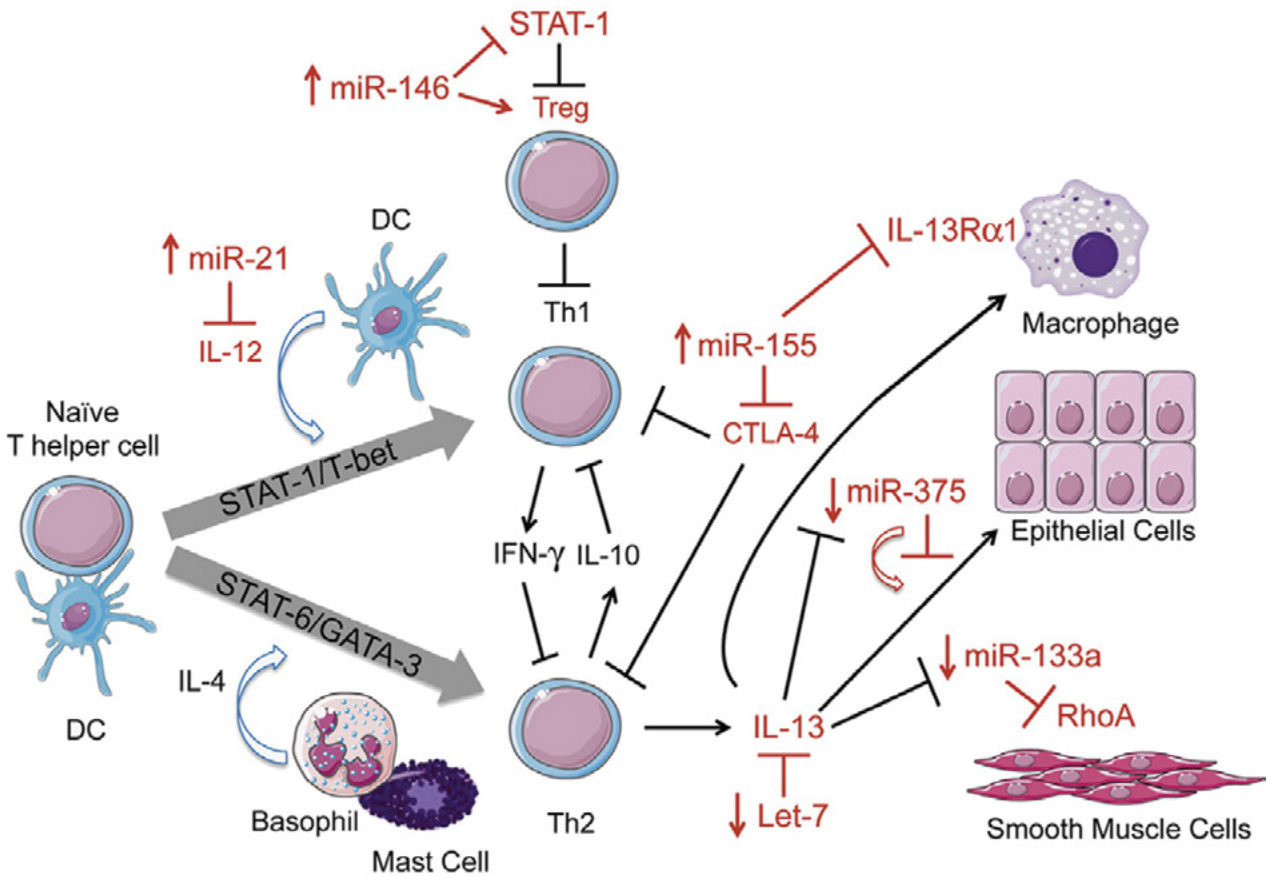

Figure 2 Sketch map depicting the recognized functions of miRNAs and their targets in allergic inflammation. miRs inhibit immune genes and cells which in turn affect Th1/Th2 balance in the allergic response. (*Reprinted from J Allergy Clin Immunol, 132/1, Lu TX, Rothenberg ME. Diagnostic, functional, and therapeutic roles of microRNA in allergic diseases, 3-13, Copyright 2013, with permission from Elsevier.*)

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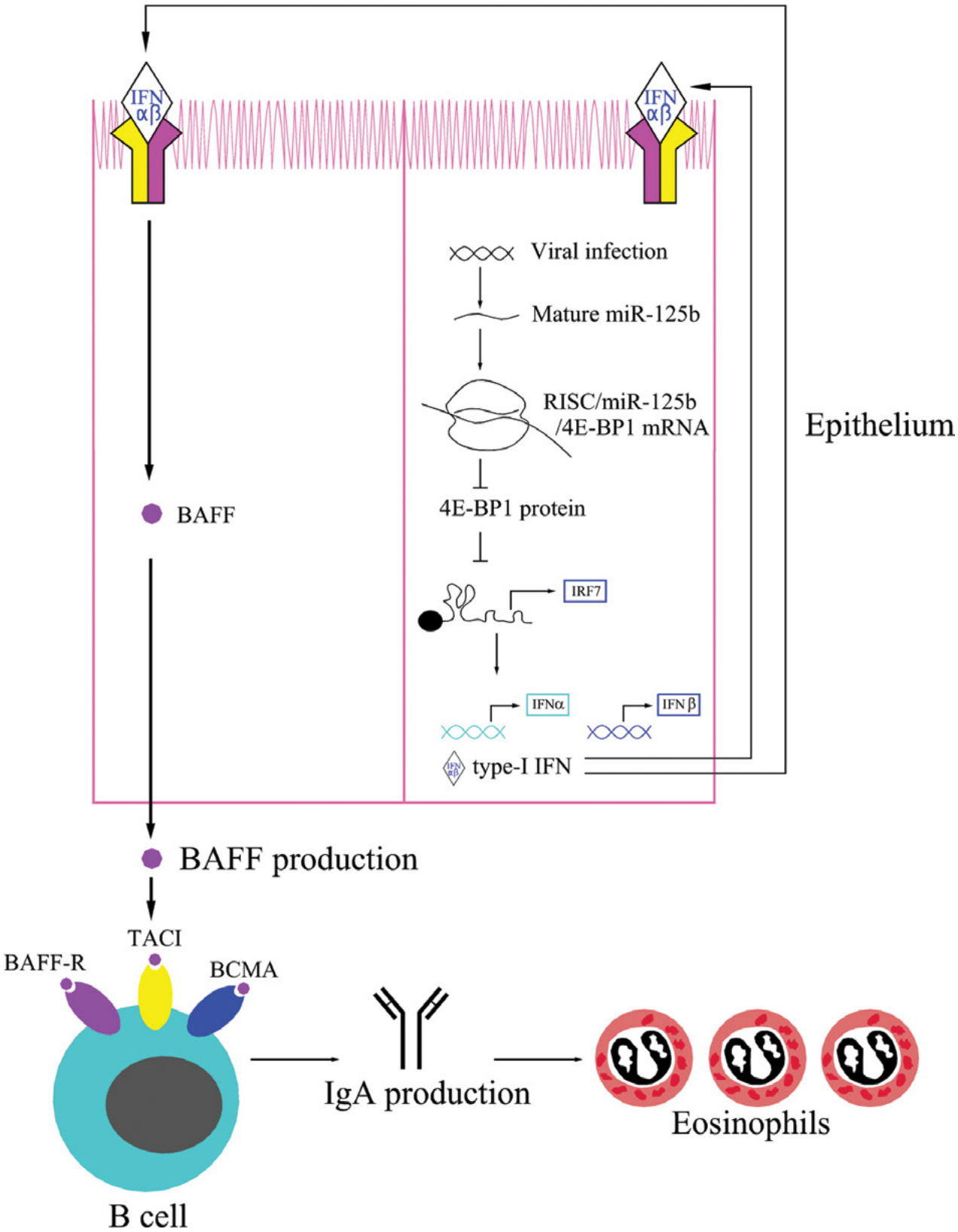
Figure 3 The role of miR-125b in eosinophilic inflammation of chronic rhinosinusitis (CRS). MiR-125b-eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1)-type I IFN pathway lead to increased production of type I IFN which induce B cell-activating factor (BAFF) secretion from epithelial cells and subsequent IgA production and local activation of eosinophils. (*From: Zhang XH, Zhang YN, Liu Z. MicroRNA in chronic rhinosinusitis and allergic rhinitis. Curr Allergy Asthma Rep 2014; 14: 415*).


IFN αβ
IFN αβ
Viral infection
Mature miR-125b
RISC/miR-125b /4E-BP1 mRNA
Epithelium
BAFF
4E-BP1 protein
IRF7
IFNα
IFN β
type-I IFN
BAFF production
TACI
BAFF-R
BCMA
IgA production
Eosinophils
B cell

16 REGULATION OF INFLAMMATION BY CELL DEATH IN ALLERGIC RHINITIS

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KEY MESSAGES

- Delayed eosinophil apoptosis contributes to tissue eosinophilia and is driven by IL-5
- Eosinophil activation leads to eosinophil cytolysis, a non-apoptotic type of cell death
- Successful therapies delete eosinophils from tissues
- Specific cell death pathways should be considered as targets for anti-allergic therapies

The regulation of cell death in allergic rhinitis (AR) has been relatively little investigated and its possible contribution to pathogenesis largely ignored. As with other types of inflammatory responses, the local accumulation of different subgroups of leukocytes occurs during the initiation and maintenance phases, whereas inflammatory cell numbers decline in the resolution phase of allergic inflammation. The changes in cell numbers during inflammation are largely due to changes in rates, both of cell recruitment and of cell death. Important leukocyte subgroups believed to play critical roles in the pathophysiology of AR are the dendritic cells, T cells, mast cells, and eosinophils.

The contribution of cell death to the pathogenesis of allergic diseases has recently been summarized elsewhere. Although most of the reports published so far have not been studies with AR patients or animal models, one could expect that these findings should have relevance for AR. For instance, it is likely that epithelial cell damage accompanies the allergic inflammation of the nasal mucosa. Moreover, the susceptibility of T cells for undergoing apoptosis might be regulated similarly to other inflammatory responses.

The mode of cell death in eosinophils has been the subject of most studies on cell death regulation and inflammation in AR. Eosinophils accumulate in the nasal mucosa not only owing to increased recruitment, but also as a consequence of delayed apoptosis. The major eosinophil survival factor seems to be IL-5. Interestingly, allergen-specific immunotherapy reduced IL-5 production by CD4+ T cells in AR patients and anti-IL-5 antibody therapy has been effective in patients with nasal polyposis. The beneficial effect of topical corticosteroid therapy in AR is probably also largely a consequence of the reduced expression of Th2 cytokines, including IL-5. Besides delayed eosinophil apoptosis, eosinophil degranulation and cytolysis, which represents a form of non-apoptotic cell death, have also been observed in AR. It has been suggested that eosinophil cytolysis occurs without prior extensive degranulation and is the result of major activation mechanisms distinct from degranulation. The molecular mechanisms of eosinophil activation resulting in cytolysis remain to be investigated.

A look at the molecular basis of many allergic diseases reveals a cell death component that either accounts for the disease or contributes to disease progression. For instance, following eosinophil activation in AR, signaling pathways mediating both cell survival and cell death are activated. Regardless the cellular response, the inflammation is maintained (Fig. 1). Therefore, current and future

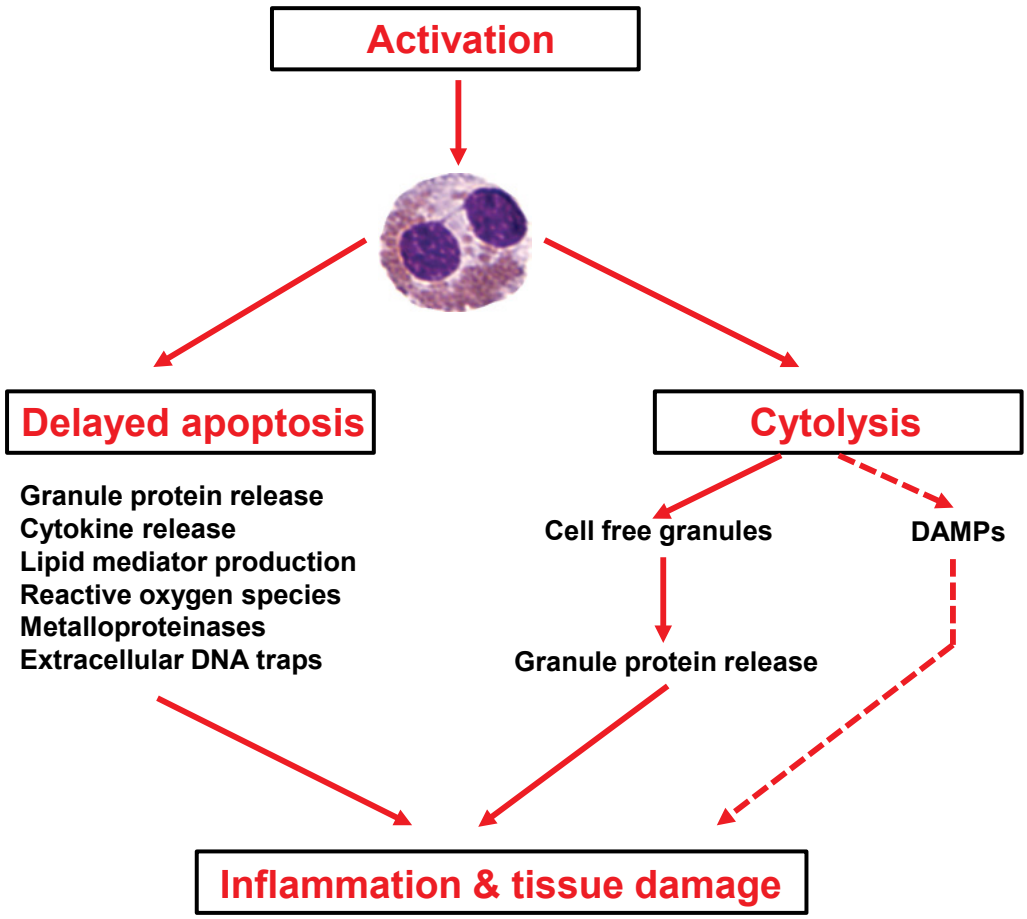

Figure 1 Eosinophil activation and their cellular life span. The activation of eosinophils can change their cellular life span. Either eosinophils exhibit a prolonged life span owing to cytokine-mediated delayed apoptosis or they undergo cytolysis. With delayed apoptosis, eosinophils contribute to the maintenance of inflammation by multiple mechanisms. Cytolysis, on the other hand, is associated with massive granule protein secretion. Moreover, cytolysis most likely results in the release of damage-associated molecular pattern molecules (DAMPs), which are known to trigger inflammatory responses. The release of DAMPs from cytolytic eosinophils remains to be further studied; hence, this pathway is indicated with dashed arrows.

anti-allergic therapies should also be analyzed with respect to their impact on cell death pathways.

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17 MECHANISMS OF IMMUNE REGULATION IN ALLERGIC RHINITIS

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KEY MESSAGES

- Allergen-specific Th2 responses are essential for induction of allergic rhinitis
- Allergen-specific immunotherapy is the only available curative treatment for allergic rhinitis
- Allergen-tolerance is mediated by tolerogenic dendritic cells (DCs), regulatory T cells and regulatory B cells
- IL-10 and TGF-beta play a key role in tolerance induction through suppression of Th2 responses and basophil/mast cell activation, as well as by skewing B cells from IgE production towards IgG4 and IgA production

Immune tolerance induction through allergen-specific immunotherapy (AIT) is currently the only curative therapy for several allergic diseases including allergic rhinitis (AR). The principle for AIT is to induce immune tolerance to an allergen through high-dose exposure for prolonged periods of time.

The mechanisms that underlie allergen tolerance include changes in dendritic cells (DCs), allergen-specific B- and T- cells, and reduced activation of effector cells such as basophils, mast cells and eosinophils. This results in suppression of both immediate and late phase responses triggered by allergen exposure.

Already within hours after the first injection of the allergenic extract used for AIT the level of mast cell and basophil degranulation in response to allergen exposure is reduced. This effect may be attributed to the gradual inhibition of degranulation that may take place during the buildup phase of AIT and to changes in histamine receptor 2 expression on basophils.

While Th2 cells are key drivers of allergic sensitization, one of the hallmarks of allergen tolerance is the induction of allergen-specific Tregs. Both inducible T regulatory type 1 (TR1) cells and FoxP3+ natural Tregs increase during allergen tolerance induction. Through the secretion of IL-10 and TGF-β, regulatory T cells can suppress T helper cell responses and the activation and migration of mast cells, basophils and eosinophils. IL-10 also limits maturation and antigen-presentation capacity and maturation of DCs. Immature plasmacytoid DCs can induce IL-10-producing TR1 cells, thereby fueling a positive feedback loop promoting tolerance. TGF-β is a pluripotent cytokine, which can suppress Th1, Th2 and B cell responses as well as IgE production, while promoting Treg responses and IgA production by B cells (Figure 1).

Dendritic cells (DCs) are key regulators of allergen-specific immune responses. In response to epithelium-derived cytokines such as IL-25, IL-33 and TSLP, allergen-loaded DCs promote Th2 differentiation. Other signals, including IL-10, vitamin D3 metabolites, retinoic acid, adenosine and histamine can prime immature or conditioned mature DCs to induce regulatory T cells (Tregs) (Figure 2).

The predominant Th2 response during allergic sensitization drives B cells to produce allergen-specific IgE. However, during tolerance induction, the production of specific IgG4 (an immunoglobulin isotype that has anti-inflammatory properties) rapidly increases. IL-10 plays an essential role in this pro-

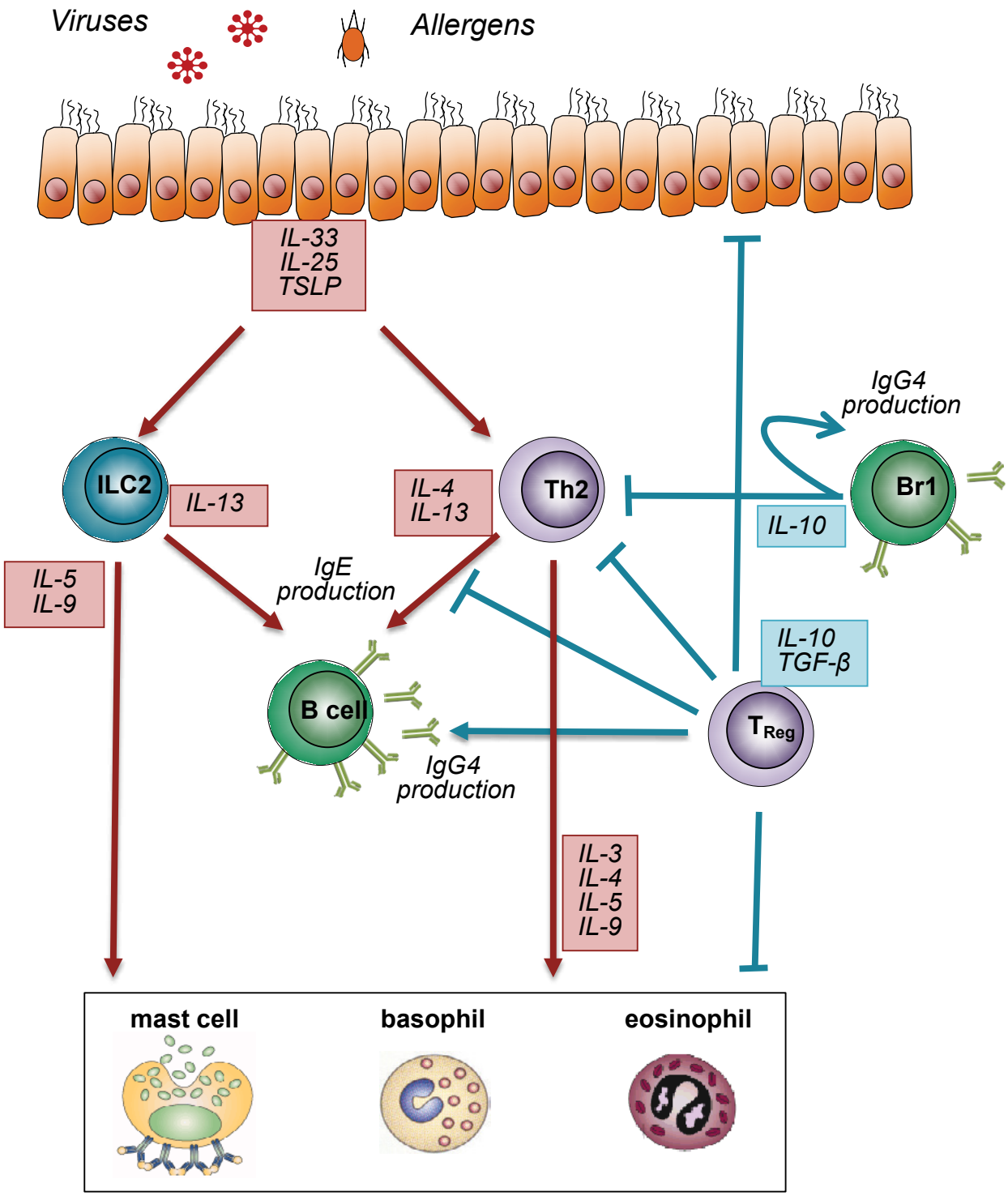

Figure 1 Role of Treg and Breg cells in the suppression of allergic inflammation. Treg cells and their cytokines mainly IL-10 and TGF-β suppress Th2 type immune responses and control allergic inflammation in many ways. Blue arrows show the regulatory and suppressive effects of Treg and Breg cells on: B cells by inducing IgG4 and IgA and suppressing IgE; on Th2 cell by suppressing proliferation and homing to tissues; on mast cells, basophils and eosinophils via direct and indirect suppressive effects.

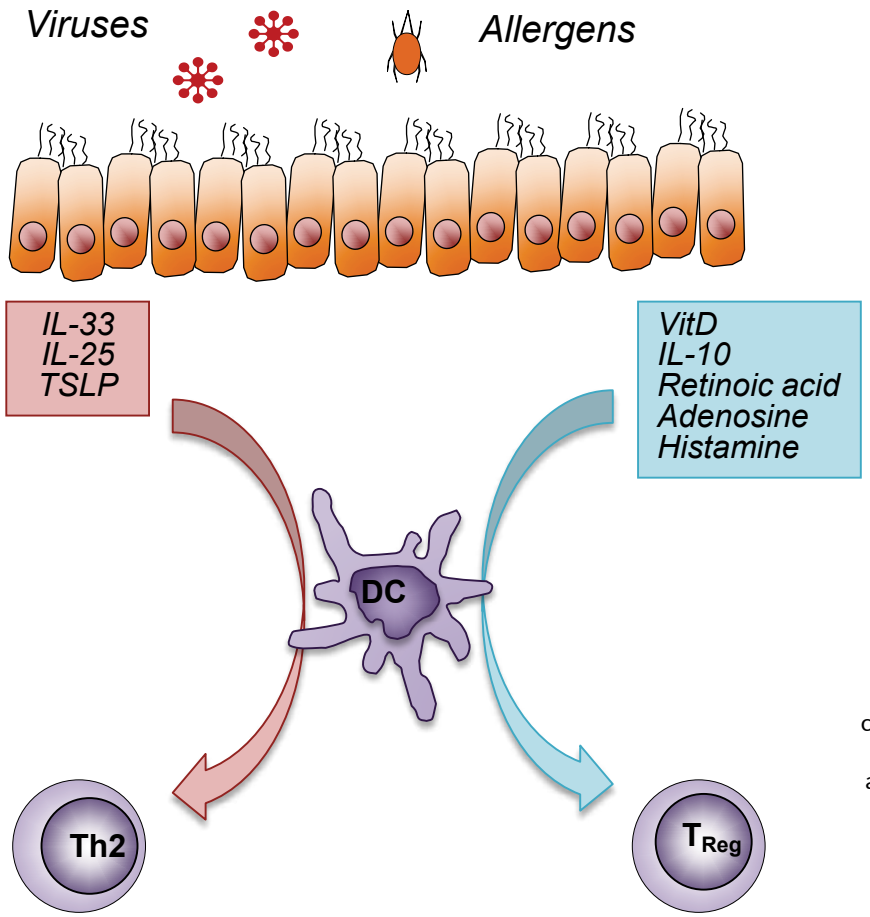

Figure 2 Distinct role of the micromilieu of dendritic cells in driving T cells differentiation. IL-33, IL-25 and TSLP promote Th2 cells differentiation through DCs. In contrast, other signals such as vitamin D3 metabolites, IL-10, retinoic acid, adenosine and histamine induce Treg cells through DCs.

cess through suppressing IgE production and enhancing IgG4 production. In addition to Treg cells, IL-10-producing B regulatory cells can potently suppress T cell proliferation and upregulate IgG4 production. The frequency of these cells is upregulated during AIT (in a bee venom immunotherapy study). Their role in the regulation of respiratory allergies remains to be determined. Thus, IL-10, which can be produced both by T- and B-cells, modulates the allergen-specific humoral response from IgE towards IgG4. The role of the recently described innate lymphoid cells (ILCs) in this intricate cellular interplay is largely unknown. A recent study demonstrated a reduction of peripheral ILC2s during the pollen season in AR patients who received AIT (Figure 1).

In conclusion, many cells and molecules play their part in the regulation of immune responses in AR and many processes remain to be further elucidated.

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18 LIPID MEDIATORS IN ALLERGIC RHINITIS: INFLAMMATION AND RESOLUTION OF INFLAMMATION

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KEY MESSAGES

- Arachidonic acid metabolites play a central role in the pathogenesis of allergic rhinitis (AR)
- Cysteinyl leukotrienes (CysLT) and prostaglandin D2 (PGD2) are potent proinflammatory mediators that are released into nasal secretions of patients with AR. The role of prostaglandin E2 in AR remains to be clarified
- Lipoxins are released into nasal secretions of patients with AR and appear to exert anti-inflammatory effects
- Antagonists of the CysLT1 receptor improve symptoms in patients with AR. The potential therapeutic effect of antagonist of the DP2 receptor of PGD2 and of lipoxin analogs remains to be demonstrated

Arachidonic acid (AA) is released from the cell membrane phospholipids by activated phospholipases A2. When AA is metabolized through the 5-lipoxygenase (5-LO) enzyme pathway leukotrienes (LT) B4 (LTB4) and cysteinyl leukotrienes (CysLT), LTC4, LTD4 and LTE4 are generated (Figure 1).

Five G protein-coupled receptors (GPCR) receptors for LT have been cloned: BLT1 and BLT2 which bind LTB4, CysLT1 and CysLT2 which bind CysLTC4 and LTD4 and CysLT3R receptor selective for LTE4 (Figure 1). Neutrophils preferentially generate LTB4, whereas mast cells, basophils and eosinophils preferentially generate CysLT.

CysLT exert multiple biological activities including recruitment of eosinophils, stimulation of airway mucus secretion and up-regulation of the inflammatory cytokines.

AA can also be converted via the cyclooxygenase (COX) pathway into prostaglandins (PG), PGE2, PGD2, PGF2alpha, PGI (prostacyclin), and TXA2 (tromboxane). Mast cells preferentially generate PGD2. There are two isoforms of COX, a basal or constitutive form (COX-1) and an inducible form (COX-2).

The role of PGs in the inflammatory response is often ambiguous. In certain settings, PGs exert inflammatory functions (PGE2, PGD2, PG2alpha, TXA2), but in others, they appear to act as anti-inflammatory endogenous molecules (PGE2, PGD2) (Figure 2).

Lipoxin A4 (LXA4) can be generated either by the sequential lipoxygenation of AA by the 15-lipoxygenase (15-LO) in epithelial cells and 5-LO in leukocytes, or by the production of LTA4 by 5-LO in leukocytes, which is converted into LXA4 by a platelet 12-LO. Lipoxins exert anti-inflammatory and pro-resolution effects through the activation of their GPCR FPRL-1.

CysLT and PGD2 are elevated in nasal fluids from symptomatic allergic rhinitis (AR) patients compared with healthy controls. In contrast, LTE4 and PGD2 levels measured in nasal biopsies were found significantly lower in AR than in controls.

Allergen nasal provocation increases CysLT, LTB4 and PGD2 release during the early phase of the nasal allergic response (1-2). CysLT concentrations also increase during the late phase response. Treatment with CysLT1 receptor

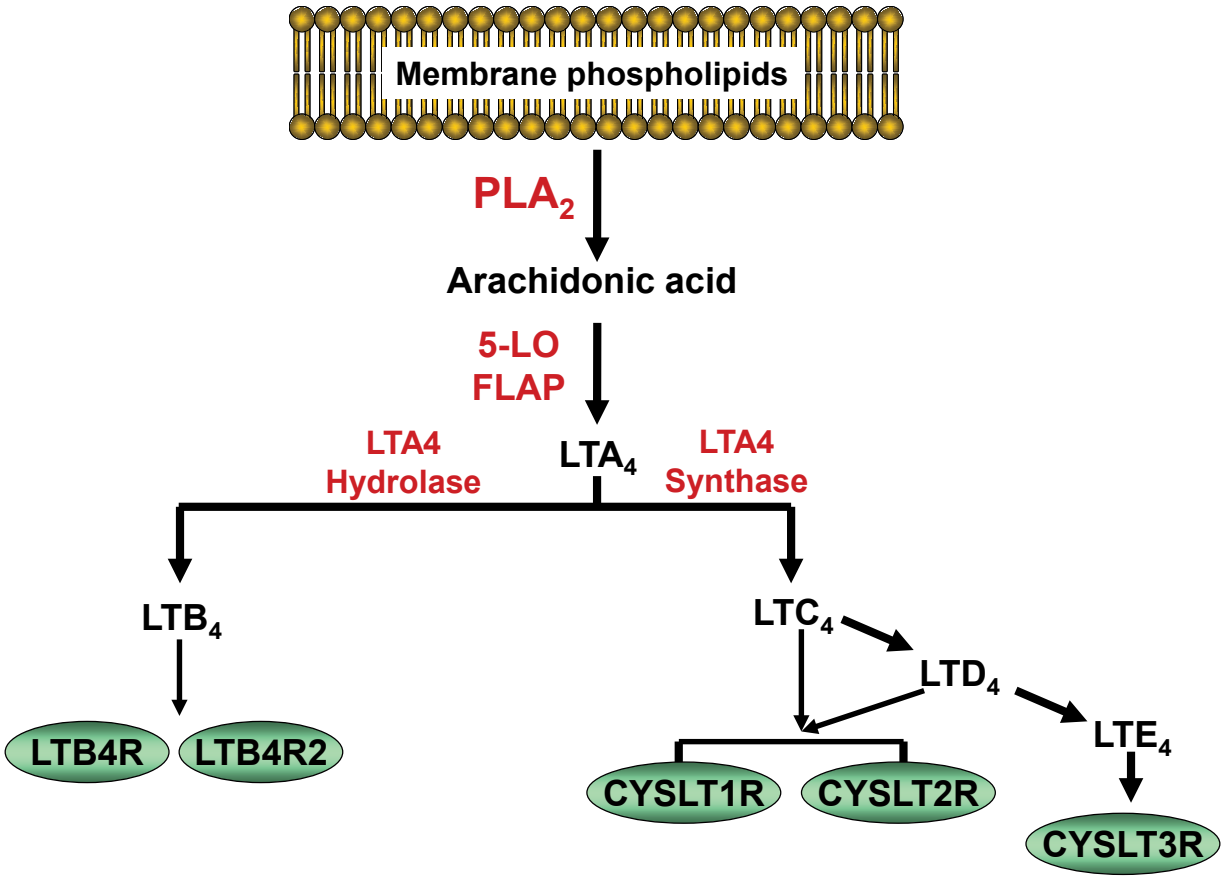

Figure 1 Arachidonic acid (AA) released from cell membrane phospholipids by phopholipase 2 can be converted by the 5-lipoxygenase-activating protein (FLAP) and the 5-lipoxygenase (5-LO) into leukotrienes (LT) A4 (LTA4), which can be further metabolized either into leukotriene B4 (LTB4) in cells that express the LTA hydrolase enzyme, such as neutrophils, or into the cysteinyl leukotrienes, LTC4, LTD4 and TLE4 in cells equipped with the LTC4 synthase such as eosinophils and mast cells. BLT1 and BLT2 receptors bind LTB4. CysLT1, CysLT2 bind CysLTC4, LTD4 and and CysLT3R binds LTE4. CysLTs are chemotactic factors for eosinophils and play an important role in the pathogenesis of allergic rhinitis especially in nasal obstruction. CysLT1 receptor antagonists can modulate nasal inflammation by inhibiting allergen-induced influx of eosinophils into the nasal mucosa.

antagonists reduces nasal symptoms (congestion, rhinorrhea, pruritus and itching). Various DP2 antagonists are currently in clinical development to treat AR.

PGE2 levels in nasal lavage fluid have been found higher, similar and lower in symptomatic AR compared to healthy controls. No changes or increased release of PGE2 have been reported after allergen nasal challenge.

Concentrations of LXA4 in lavage nasal fluid are higher in patients with AR rhinitis compared with controls. LXA4 inhibits release of inflammatory mediators such as interleukin 8 and tumor necrosis alpha. LXA4 analogs can be potential regulators of inflammation in AR.

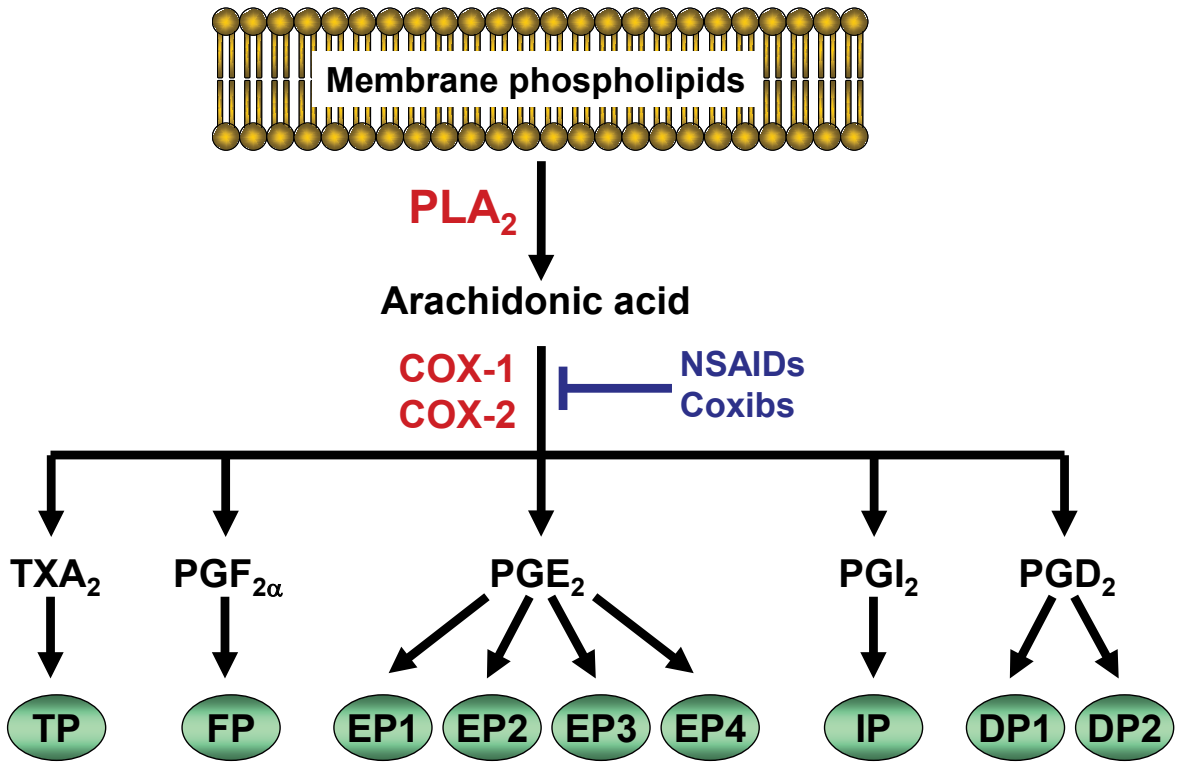

Figure 2 Prostanoids are derived from AA by the action of cyclooxygenases (COX). COX-1 exerts physiological functions while COX-2 is upregulated in inflammation. Prostanoids can be subdivided into three groups: prostaglandins, prostacyclins and thromboxanes. They are synthesized by specific enzymes and interact with nine PG receptors named by the letter "P" and a prefix of "D", "E", "F", "I", or "T" to signify preference for PG. Four subtypes receptors (EP1-EP4) are described for PGE2, two for PGD2 (DP1 and DP2), one for PGF2alpha (FP), prostacyclin (IP), and thromboxane A2 (TXA2) respectively. PG receptors belong to G protein-coupled receptors. Under normal conditions prostanoid levels in cells are low but during inflammation the nature and concentrations of protanoids can change dramatically. Prostanoids are viewed as part of complex regulatory networks of inflammation. The potential therapeutic effects of DP2 receptor antagonist in allergic rhinitis is currently being investigated.

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19 THE EPITHELIAL BARRIER IN THE NOSE

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KEY MESSAGES

- The epithelium in upper airways is the first line of defence against extrinsic agents including bacteria, pollen and other pathogens
- The epithelial barrier may become disrupted by different agents including pollens and proinflammatory cytokines
- The epithelial-derived thymic stromal lymphopoietin (TSLP) may preserve the epithelial barrier and induce tight junctions between dendritic cells during the early stage of allergic rhinitis (AR)
- In severe AR, marked upregulation of TSLP and disruption of the epithelial barrier are observed

The epithelial barrier in upper and lower airways forms the first line of defence against intruding allergens, pollutants and pathogens. It is therefore a prerequisite to maintain an intact and functioning epithelium in order to keep the submucosal equilibrium balanced and not to promote inflammation. The epithelial barrier in the nose and paranasal sinuses consists of a pseudostratified, ciliated, epithelium that is held together by structures like tight junctions, desmosomes, adherens junctions and gap junctions. Furthermore, barrier function is promoted by proteins that have antimicrobial properties such as defensins, cathelicidins, lysozyme and lactoferrin, as well as others. The S-100 protein family contributes to these antimicrobial effects, while influencing innate immunity and Toll-like receptors (Figure 1).

One of the main contributors to the barrier function is the tight junctional belt. Tight junctions are formed by the integral membrane proteins Claudins, Occludin, lipolysis-stimulated lipoprotein receptor (LSR) and junctional adhesion molecules (JAMs,) and by many peripheral membrane proteins, including the scaffold PSD95-Dlg-ZO1 (PDZ)-expression proteins Zonula occludens and the non-PDZ -expressing proteins. These tight junctions are controlled by various cytokines and growth factors via distinct signal transduction pathways. The tight junction molecules are expressed in both membranous or microfold cells (M cells) and dendritic cells (DCs) as well as by the epithelial cells of upper airways (Figure 2). Various antigens are sampled, transported, and released to lymphocytes through the cells in nasal mucosa, while they maintain the integrity of the barrier. Expression of tight junction molecules and the barrier function in normal human nasal epithelial cells (HNECs) are affected by various stimuli including growth factors, TLR ligands and cytokines etc (Table 1). In addition, epithelial-derived thymic stromal lymphopoietin (TSLP) which is a key factor for allergic inflammatory diseases including allergic rhinitis (AR), enhances the barrier function together with an increase of tight junction molecules in HNECs and DCs (Figure 3). In severe or chronic AR, marked upregulation of TSLP and disruption of tight junctions are observed (Figure 3). Pollens and their proteolytic enzymatic properties are capable of disrupting tight junctions facilitating their intrusion. Upper airway epithelium has been shown to have an increased permeability in

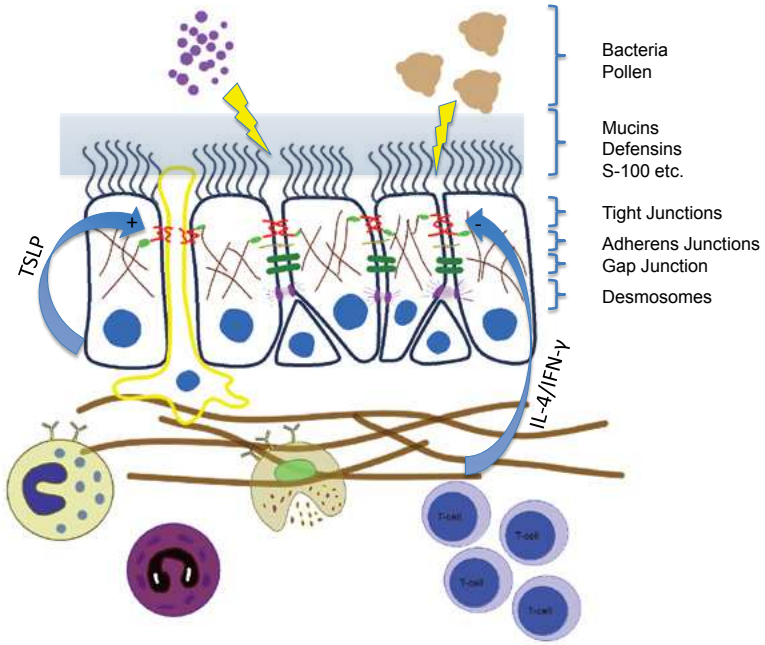

Figure 1 The nasal epithelial barrier and influencing agents.

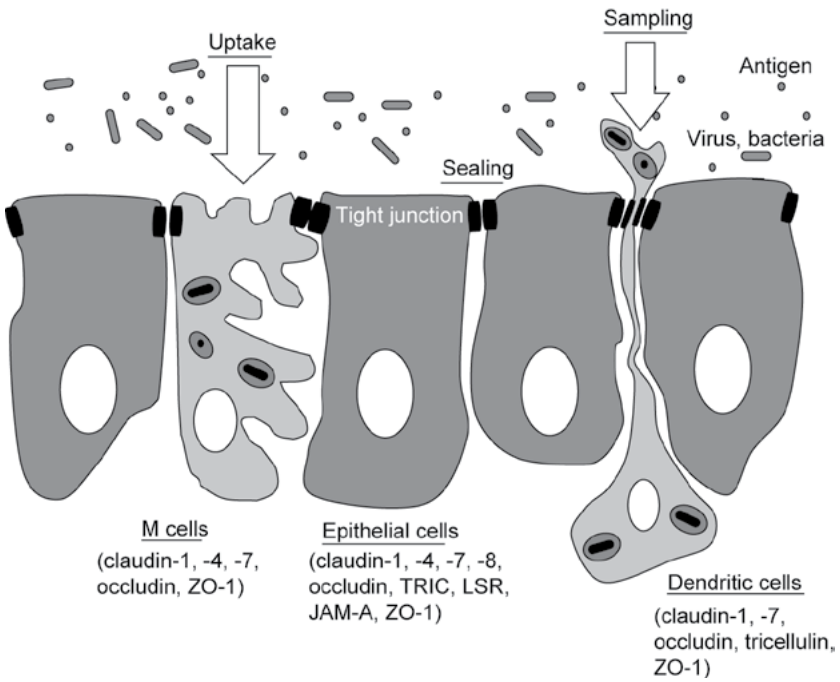

Figure 2 Putative sealing intercellular spaces by tight junction molecules in the upper airway epithelium including epithelial cells, M cells and dendritic cells. (*From Kojima T, Go M, Takano K, Kurose M, Ohkuni T, Koizumi J, et al. Regulation of tight junctions in upper airway epithelium. Biomed Res Int 2013;2013:947072.*)

Th2 driven inflammation of chronic rhinosinusitis with polyps and leakiness of sino-nasal epithelial cell cultures was promoted by IL-4 and IFN-g. This is in line with other research results from Th2 driven inflammatory conditions such as asthma. Further studies of the epithelial barrier in upper airways should provide new insights not only into pathological conditions in AR but also to provide new therapeutic targets.

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TABLE 1

Changes of tight junction proteins and barrier function in HNECs in vitro

Intervention		Tight junction proteins	Barrier function
Fetal bovine serum		CLDN-1↑; CLDN-4↑	upregulation
Growth factor	TGF-β	CLDN-4↑	no change
PKC activator	TPA	CLDN-1↑; OCLN↑; ZO-1↑; ZO-2↑	upregulation
PPARγ ligands	Rosiglitazone	CLDN-1↑; CLDN-4↑; OCLN↑; TRIC↑	upregulation
	Troglitazone	CLDN-1↑; CLDN-4↑; OCLN↑	
TLR3 ligand	Poly I:C	JAM-A↓	no change
Allergen	Der P 1	CLDN-1↓, JAM-A↓	downregulation
Virus	RSV	CLDN-4↑; OCLN↑	upregulation
Bacteria	Pseudomonas aeruginosa elastase	CLDN-1↓; CLDN-4↓; OCLN↓; TRIC↓	downregulation
microRNA	miR-146a mimic	CLDN-1↑; OCLN↑; JAM-A↑	upregulation
GJIC activator	Irsogladine maleate	CLDN-1↑; CLDN-4↑; JAM-A↑	upregulation
Cytokine	IL-4	OCLN↓, ZO↓	downregulation
Cytokine	IL-17a	no changes observed	no change
Cytokine	IFN-g	stratification	downregulation
Cytokine	TSLP	CLDN-1↑; CLDN-4↑; CLDN-7↑; OCLN↑	upregulation

Abbreviations: CLDN = claudin; Der p = Dermatophagoides pteronyssimus; GJIC = Gap junction intercellular communication; IFN = interferon; IL= interleukin; JAM = junctional adhesion molecules; OCLN = occluding; PKC = protein-kinase C; PPAR = Peroxisome proliferator-activated receptor; RSV = respiratory syncytial virus; TLR = Toll-like receptor; TSLP = epithelial-derived thymic stromal lymphopoietin; TGF-β= transforming growth factor β; TPA= 12-O-tetradecanoyl-Phorbol-13-acetate; TRIC = tricellulin; ZO = zonula occludens

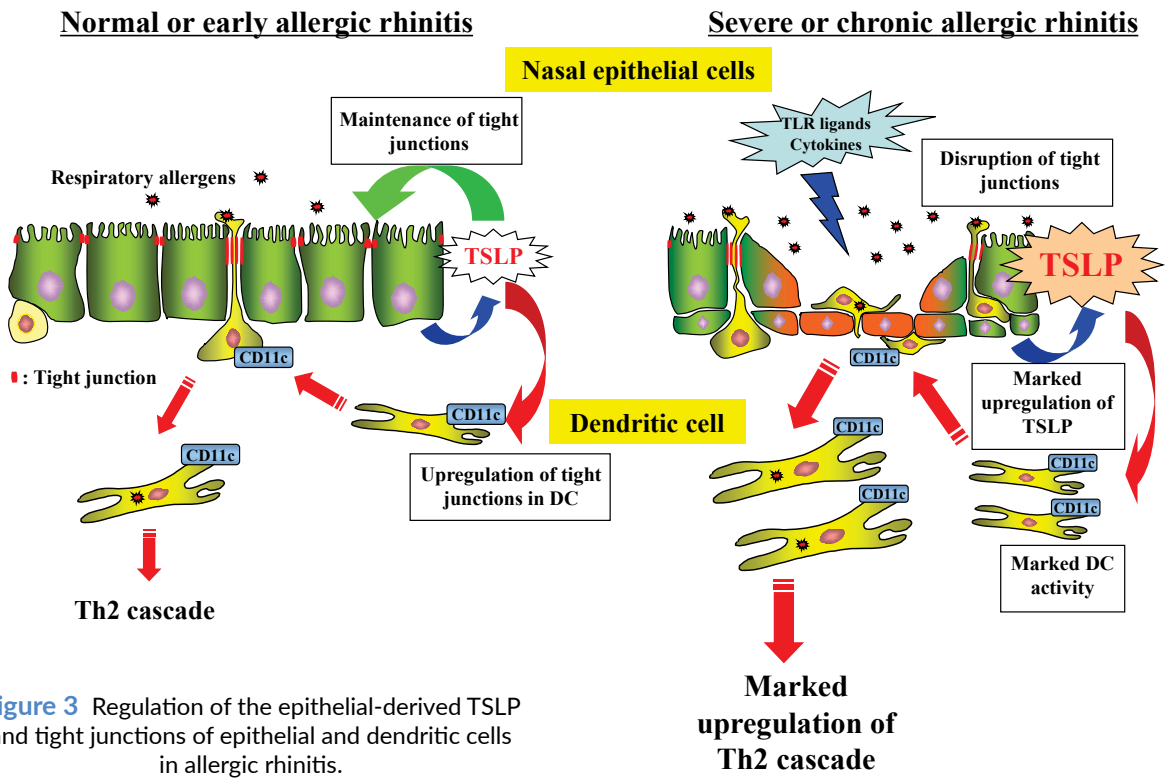

Figure 3 Regulation of the epithelial-derived TSLP and tight junctions of epithelial and dendritic cells in allergic rhinitis.

20 NEURO - IMMUNE MECHANISMS IN ALLERGIC RHINITIS

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KEY MESSAGES

- The sensory innervation of the nose conveys sensations of itch, airflow (epithelial cooling), irritation (nociception), and possibly congestion due to venous sinusoid dilation
- Histamine stimulates H1 receptors on type C neurons to induce itch
- Histamine – independent itch may contribute to persistent allergic rhinitis
- Itch is mediated by a subset of pain neurons
- Allergic inflammation is likely to modify afferent receptors, combinations of neurotransmitters, and spinal cord dorsal horn central sensitization that mediates neuropathic itch
- Itch pathways can interfere with cognition leading to disability and allergic fatigue

ITCH – PAIN NERVES

Unmyelinated Type C trigeminal neurons innerve the nasal epithelium (Figure 1). These highly branched nerve endings also extend to submucosal gland acini. Arteriovenous anastomoses of venous sinusoids are innervated by sympathetic neurons. Sinusoidal walls are richly innervated but their neural regulation is poorly understood. Filling of sinusoids determines obstruction to airflow and the nasal cycle.

Histamine stimulates H1-receptors to depolarize an "itch" sub-population of pain-conveying (nociceptive) neurons to cause the pruritus of allergic rhinitis (AR). Histamine – independent itch induced by protease activated receptors and other mediators occurs in chronic diseases including eczema, but this mechanism is not well studied in the human nose.

Co-localized neurotransmitters include calcitonin gene related peptide (CGRP), a potent vasodilator; neuromedin B (NMB, closely related to gastrin releasing peptide (GRP); the tachykinins neurokinin A (NKA) and substance P (SP) that are more potent for glandular exocytosis; and possibly glutamate, an excitatory amino acid neurotransmitter. In human nasal mucosa, neural depolarization by hypertonic saline stimulates axonal transmission of pain to the spinal cord and local release of neuropeptides from the branched nerve endings. This axon response stimulated seromucous gland exocytosis. Local CGRP release may stimulate plasma exudation from the most superficial sub-basement membrane vessels, but does not appear to cause venous sinusoid filling or nasal obstruction. This is unlike rodents that have few glands and stronger vascular responses to neuropeptides.

Patterns of immune and epithelial cell gene expression and allergic mediator release differ between seasonal and perennial AR. Mediators such as leukotriene B4 and nerve growth factor significantly influence sensory receptor, neurotransmitter, and inhibitory autoreceptor expression. The range of afferent sensitivity is increased by expression of endothelin and bradykinin receptors, and the trio of transient receptor potential vanilloid 1 (TRPV1), purinergic P2X receptors and acid sensing ion channel 3 (ASIC3). The trio responds to ATP, adenosine, H^+,

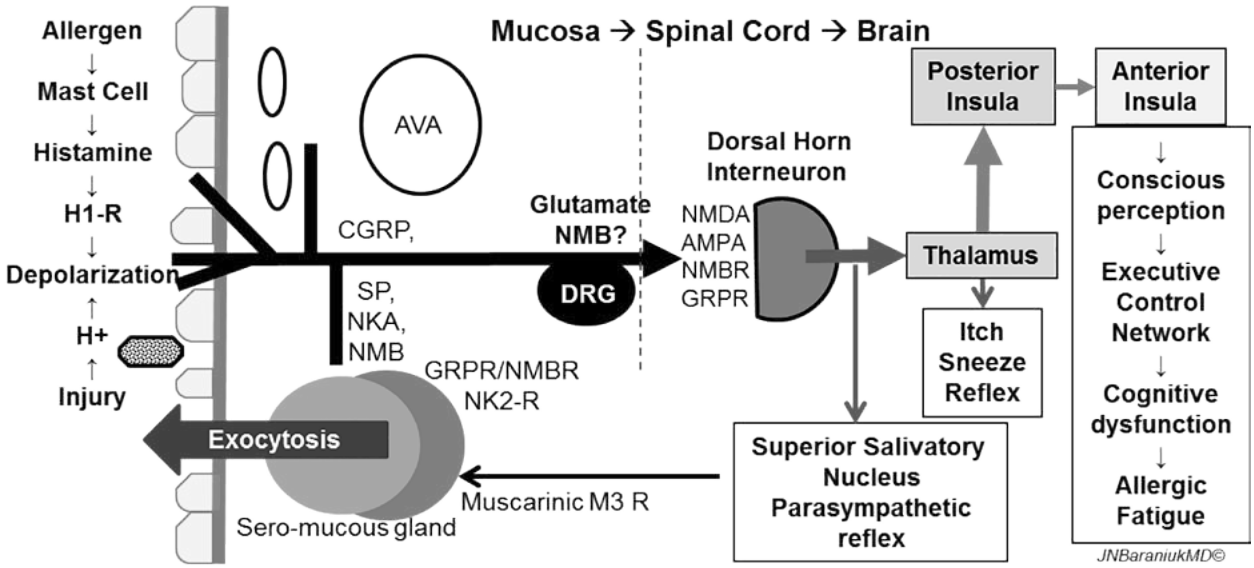

Figure 1 Histamine-sensitive itch nerves in nasal mucosa. Itch-pain Type C neurons (black line) are depolarized in the epithelium by histamine and other mediators. They release co-localized CGRP, SP, NKA and NMB in the mucosa by the axon response that leads to glandular exocytosis in humans. Glutamate is likely the predominant neurotransmitter at secondary spinal cord dorsal horn neurons. Sensation is conveyed via spino-thalamic and thalamo-cortical tracts. Itch enters conscious perception in the anterior insula, that in turn leads to cognitive dysfunction and allergic fatigue. Significant reflexes include the brainstem parasympathetic arc causing seromucous rhinorrhea, and supratentorial itch - sneeze reflex.

K^+, and Ca^{+2} released from injured cells. Neural plasticity may also contribute to mucosal hyperalgesia in idiopathic nonallergic rhinopathy. Glucocorticoids may reverse some neuronal plasticity effects indirectly by inhibiting cytokine and mediator release.

Aδ NEURONS

Thinly myelinated Aδ neurons express "cool," menthol-sensitive transient polarization receptor melanostatin 8 (TPM8) ion channels. Inhalation of ambient air evaporates water from the epithelial lining fluid. This cools the epithelium and activates Aδ afferents. Their brainstem connections help control the work of breathing and sense of dyspnea.

CENTRAL CONNECTIONS

Itch and nociceptive neurons enter the pons, turn caudally in the trigeminal spinal tract and terminate on dorsal horn pars caudalis interneurons of the first three cervical segments. Glutamate may depolarize the interneurons via N-methyl-D-aspartic acid (NMDA) receptors. Under normal conditions, these interneurons are difficult to depolarize. However, prolonged glutaminergic depolarization of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) ion channels overcomes the normal "blocked gate" activity, and allows interneuron depolarization and increased responsiveness to co-released peptide neurotransmitters. This subacute process of "central sensitization" also attenuates the ability of brainstem descending opioid and noradrenergic anti-prurinergic neurons to prevent interneuron depolarization.

Itch interneurons may use GRP as a neurotransmitter. They cross the midline, enter the lateral trigeminothalamic tract, and terminate in the medial thalamus. Axonal branches innerve the superior salivatory nucleus and recruit bilateral parasympathetic reflexes. These reflexes stimulate muscarinic M3 receptor-mediated gland exocytosis and seromucous rhinorrhea in AR, and explain the benefits of anticholinergic nasal drugs. The sneeze reflex is a complexly orchestrated response to clear the nasal airway of irritants (Figure 2).

The concept of "Allergic Fatigue" is attributed to Melvyn Danzig (1989). Tertiary thalamic nerves convey mucosal sensations to the "interoceptive cortex" in the posterior insula. Based on pain models, summation of pruritogenic messages eventually leads to activation of the anterior insula where the sensation of nasal itch becomes perceived by the con-

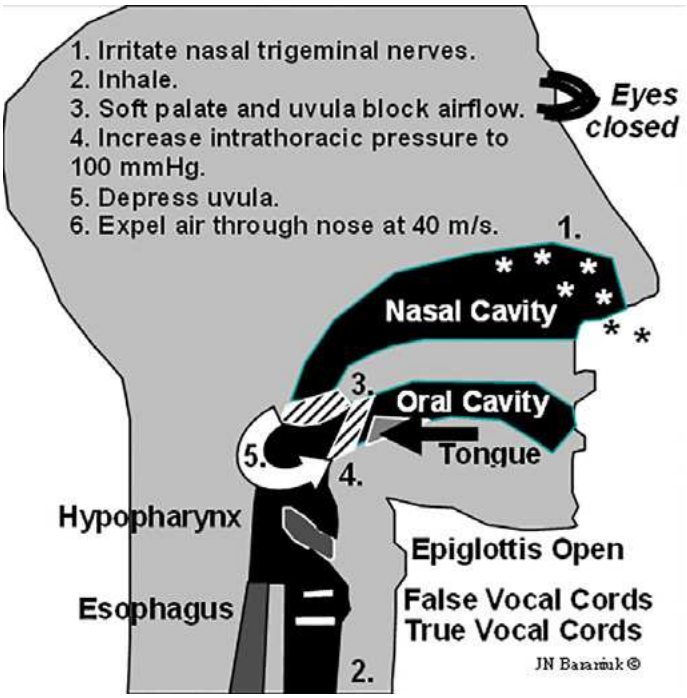

Figure 2 The sneeze. Irritation of nasal afferents (1) leads to a large inhalation (2). The soft palate, uvula and tongue move to occlude the hypopharynx and occlude the efflux of air (3) as thoracic muscles contract and increase intrathoracic pressure (4.). The uvula is suddenly depressed (5) and the column of air is forcefully expelled with high speed and shearing forces through the nasopharynx and cavities. Applying pressure to the nasal columella early in the sequence can abort the sneeze reflex.

scious mind. These perceptions interfere with salience and executive control brain networks, and explain the negative impact of AR on school or work performance and on other cognitive functions. Anterior insula efferent pathways activate brainstem sympathetic (right insula) and parasympathetic (left insula) autonomic discharges.

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21 NASAL HYPERREACTIVITY

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KEY MESSAGES

- Nasal hyperreactivity is defined as 'increased sensitivity of the nasal mucosa to commonly encountered nonspecific stimuli'
- Nasal mucosal epithelial cells, nasal vascular and glandular tissues, and neuromodulatory systems as well as other different mechanisms are involved in nasal hyperreactivity
- Cold dry air provocation tests are useful adjunct tools for the evaluation of nasal hyperreactivity

CONCEPT AND DEFINITIONS

Many patients with rhinitis often suffer from aggravation of their nasal symptoms after exposure not only to allergenic stimuli, such as house dust mites, pets, or fungi, but also to non-allergenic, non-specific stimuli, such as cigarette smoke, cold air, perfume, or air pollutants. This increased sensitivity of the nasal mucosa to commonly encountered nonspecific stimuli is defined as "nasal hyperreactivity."

PATHOPHYSIOLOGIC MECHANISMS

Although there is still much to be elucidated, it is assumed that different tissues such as the nasal mucosal epithelial cells, nasal vascular and glandular tissues, and neuromodulatory systems as well as other different mechanisms are involved in nasal hyperreactivity. As the first step, damage to the epithelium and increased epithelial permeability affect the afferent sensory nerve endings and trigger the release of several mediators (such as histamine) from mucosal mast cells. Increased sensitivity of the sensory nerve ending itself augments hyperreactivity. Additionally, the increase in the levels of non-adrenergic non-cholinergic neurotransmitters (such as neuropeptide Y and vasoactive intestinal peptide) may activate the cholinergic system and cause vasodilation of the nasal vasculature, increasing secretion from nasal glands and aggravating symptoms such as nasal stuffiness and post-nasal drip.

CLINICAL ASSESSMENT

Provocation tests using various substances have been used to evalaute nasal hyperreactivity. Pharmacologically active substances used for nasal provocation include histamine and methacholine. Cold dry air (CDA) is an example of a non-pharmacologic physical stimulus. In order to quantify the changes induced by provocation inside the nasal cavity various methods can be used, ranging from nasal symptoms scores to rhinomanometry, peak flowmetry, and acoustic rhinometry. However, there is still no widely accepted single provocation method or diagnostic standard.

CDA provocation has been proven to be superior to histamine provocation in clinical settings and correlates well the provocation tests using histamine or methacholine. The machinery for creating CDA could be simply made using a refrigerator, a pressure regulator, and a mist separator (Figure 1). By performing acoustic rhinometry before and after the provocation, changes in the volume and dimensions of the nasal cavity induced by CDA can be measured. and are reliable diagnostic criteria for the diagnosis of nasal hyperreactivity.

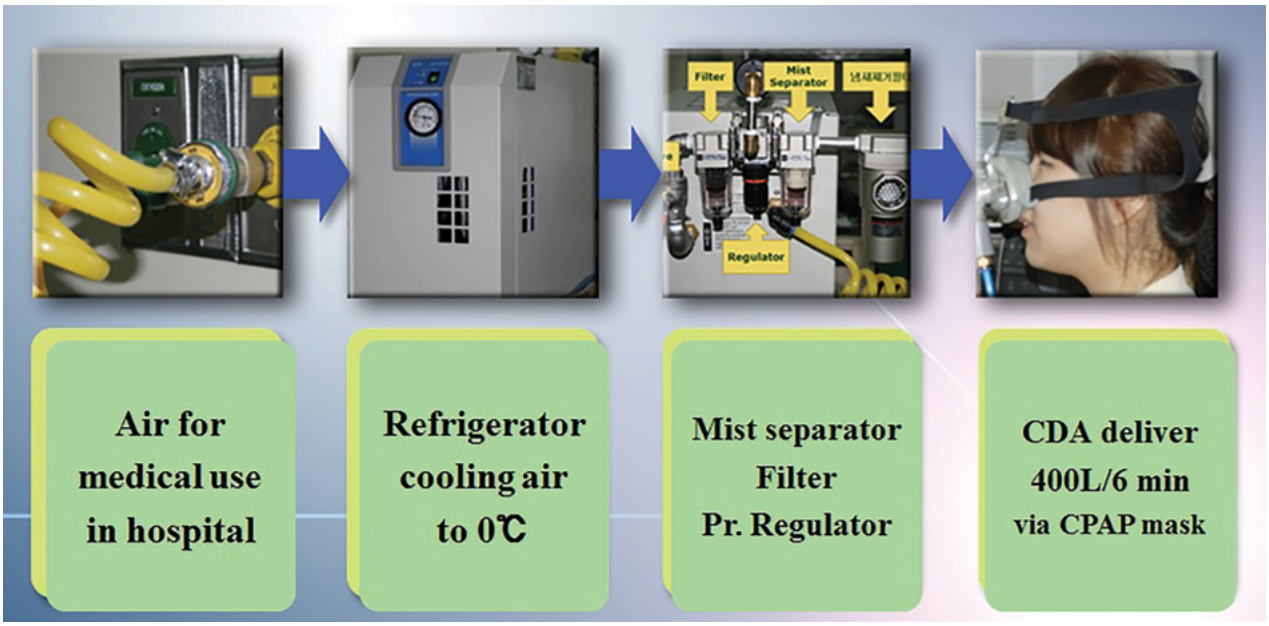

Figure 1 Cold dry air (0°C, <10% of relative humidity) can be produced by passing air through a refrigerator, a mist separator, and filters. Cold dry air is supplied to patients' nose using pediatric CPAP (Continuous Positive Airway Pressure) masks (approximately 400 L in 6 minutes).

CONCLUSION

Nasal hyperreactivity is a very common phenomenon among patients with allergic or non-allergic rhinitis. Although it significantly impairs their quality of life, we know very little about its mechanism and there are no standard diagnostic criteria or therapeutic strategies. Therefore, more studies are needed to better understand this phenomenon.

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22 ANIMAL MODELS OF ALLERGIC RHINITIS

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KEY MESSAGES

- New and improved animal models are being established for allergic rhinitis (AR)
- Animal models are particularly useful for identifying novel cellular and molecular immunological mechanisms of AR
- No single animal model completely recreates all the aspects of AR

Animal models have been developed for almost all types of allergic disease such as allergic rhinitis (AR), asthma, food allergy and anaphylaxis, atopic dermatitis and allergic conjunctivitis. These animal models are important to examine the mechanism of the disease and define the pathogenic pathways, such as the activity of genes and cellular pathways, explore the role of environmental factors (such as the microbiota), suggest new therapeutic options and predict the safety of new drugs or chemicals before being used in clinical studies, The ideal animal model should reflect the disease pathophysiology as closely as possible and new models are essential for the development of new therapies.

Laboratory mice do not spontaneously develop AR and a range of sensitization and challenge protocols have been developed. The number of sensitizations and challenges can vary, but typically animals are sensitized to the allergen via intraperitoneal injection followed by intranasal allergen challenge. Disease severity measures include sneezing frequency, nose rubbing motion frequency and nasal tissue histology. Nasal lavage fluid and nasal tissue are utilized to determine local cytokine levels and analyze the type of inflammatory infiltrate and lymphocyte polarization. AR can be influenced by the genetic background of the mice, the allergen, type of the sensitization and challenge protocol and contamination of the allergen with stimulating substances (e.g. LPS). Certain protocols require the combination of allergen with an adjuvant, for example aluminium hydroxide (ALOH3, Alum). Of note, the dosage form of Alum adjuvant is decisive. The inclusion of Staphylococcus aureus enterotoxin B is thought to support the formation of nasal polypoid lesions. The sensitization, challenge and analysis parameters of murine allergy models are summarized in Figure 1.

Although murine models of AR provide important insights into the disease mechanisms, there are some limitations that should be considered. In addition to the genetic and physiological differences between humans and mice, rats or rabbits, there are also limitations due to complexity of this disease. One can replicate important components of the disease, but no single model accurately models all the features of AR. This is very important to take into account when choosing the correct model to address the specific experimental question. For example, chronic exposure to the allergen may be required to examine many of the structural changes associated with AR. Notwithstanding the limitations of these models, several studies carried out in animal models have given important clues that explain the pathophysiological conditions related to the disease status. For instance, the role of Th2 type cytokines and T

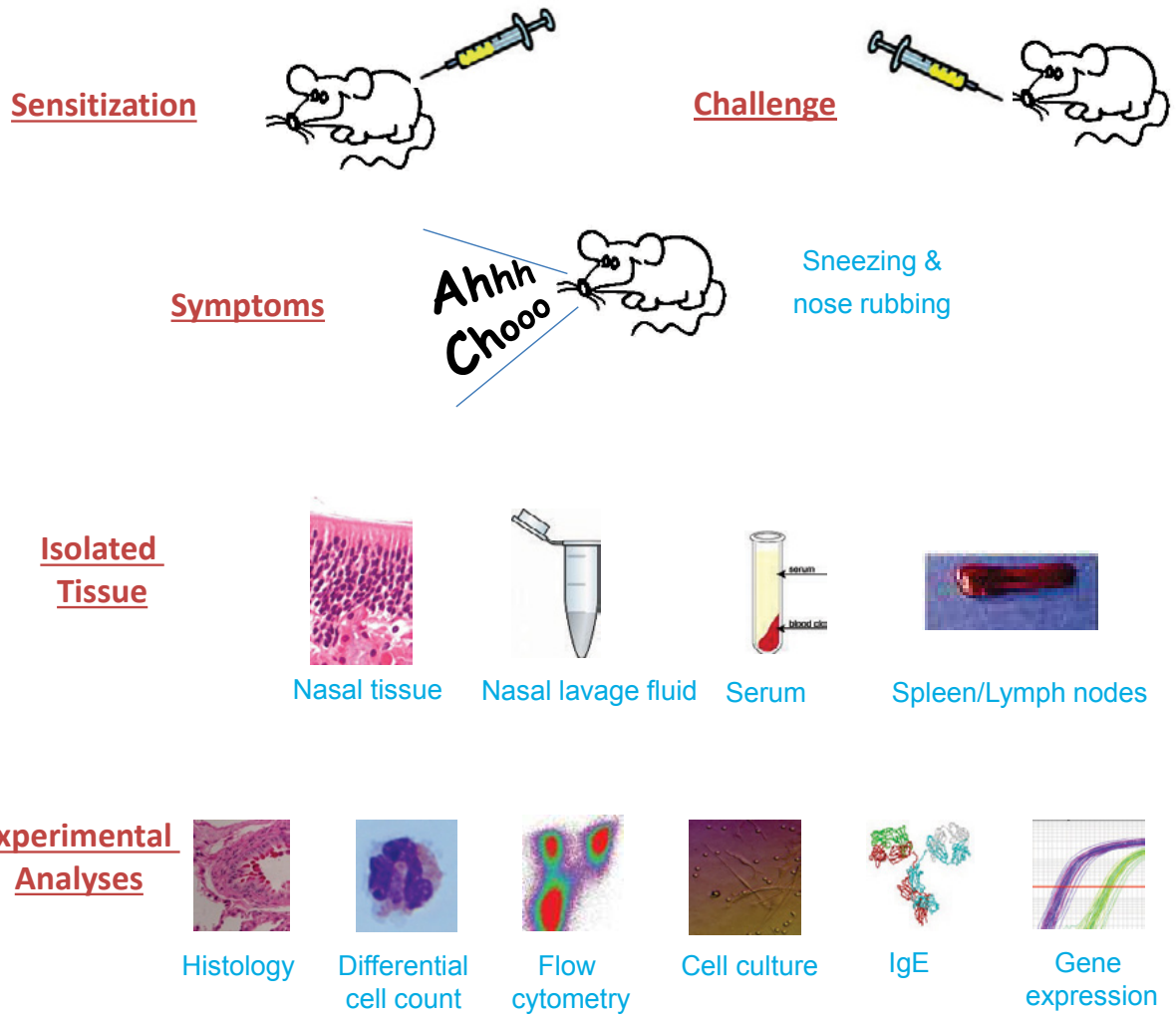

Figure 1 Overview of the experimental steps commonly used in allergic rhinitis models. Animal models typically comprise a sensitization, a challenge, and an analyses phase. After sensitization, allergic responses are provoked by intranasal application of the allergen. The severity and mechanisms of the allergic response are determined using a variety of approaches.

regulatory cells in the pathogenesis of allergy have been particularly well-studied in animal models.

Human clinical studies remain the gold standard for determining the clinical efficacy of new therapeutic approaches. Murine models will continue to provide important mechanistic clues, while improved models may extend our understanding of the basic mechanisms for examining new therapeutic options.

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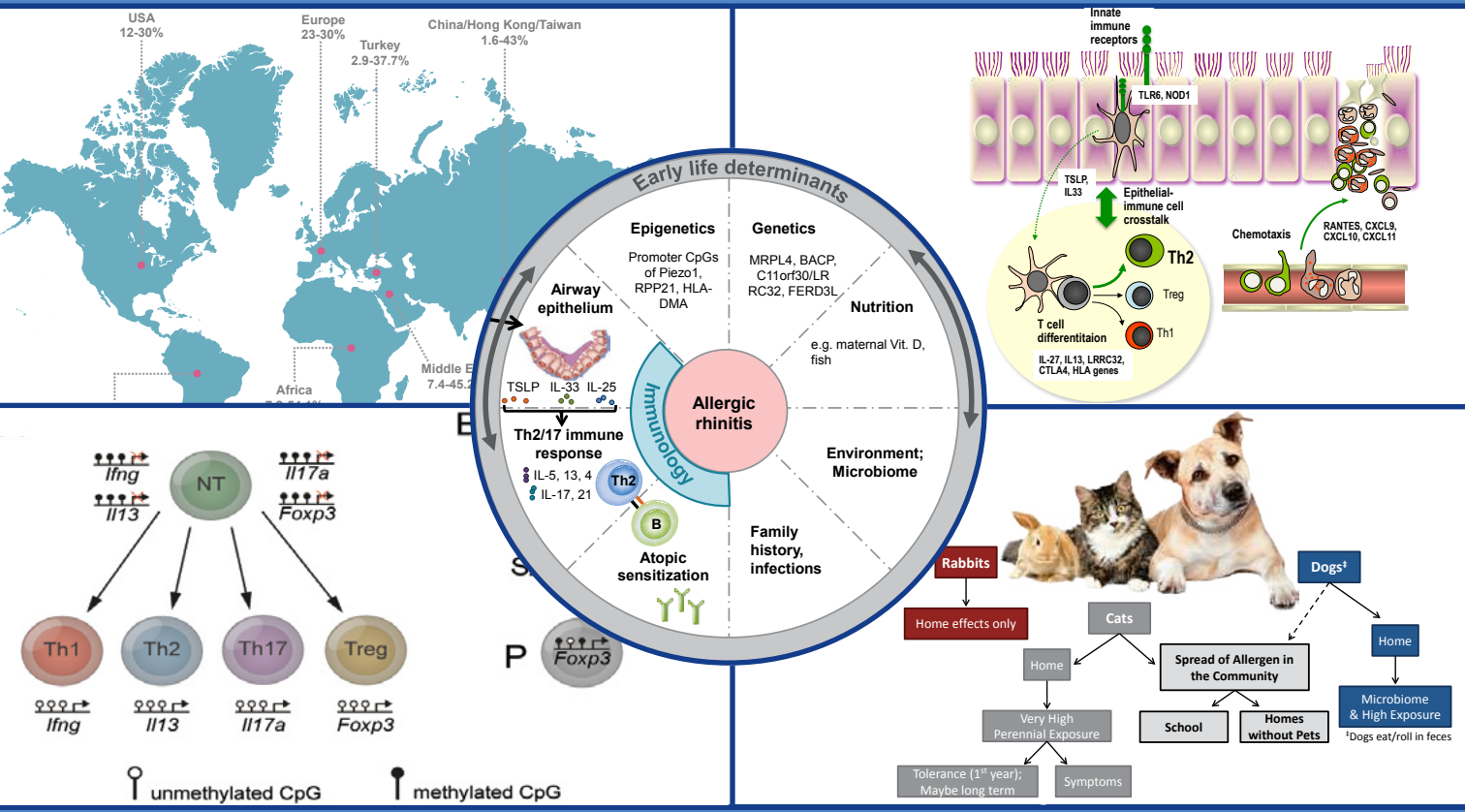
Section B



ALLERGIC RHINITIS - EPIDEMIOLOGY AND RISK FACTORS

* Epidemiology of allergic rhinitis throughout the world
* Natural history of allergic rhinitis
* Birth cohorts studies in allergic rhinitis
* Genome-wide association studies in allergic rhinitis
* Epigenetic mechanisms in allergic rhinitis
* From gene expression measurements to epidemiologic studies
* Perinatal influences on the development of allergic rhinitis
* The farm effect and allergic rhinitis
* Vitamin D and allergic diseases
* The environment-pathogen-host axis in allergic rhinitis
* The nasal microbiome
* Upper respiratory tract infections in childhood are linked to the development of allergic rhinitis in atopic children
* The common cold in allergic individuals
* Furry animals – risk or protective factor for allergic rhinitis?
* Allergic rhinitis prevalence and climate change: a global ecologic analysis
* Environmental risk factors for allergic rhinitis – home environment
* Environmental risk factors for allergic rhinitis - Work environment
* Environmental risk factors for allergic rhinitis - indoor and outdoor pollution

1 EPIDEMIOLOGY OF ALLERGIC RHINITIS THROUGHOUT THE WORLD

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Allergic rhinitis (AR) affects up to 40% of the population worldwide. High prevalence is being recorded in the developed nations of the Northern Hemisphere, with 23-30% affected population in Europe and 12-30% in the USA. Great diversity of prevalence is found in the non-Western populations of the Southern Hemisphere, with wide inter- and intra-regional variations ranging from 2.9% to 54.1% between countries. Figure 1 shows the reported prevalences of different countries, albeit without a uniform definition of AR.

KEY MESSAGES

- Global rising trend of allergic rhinitis (AR) has been observed in the past decades. The prevalence vary widely particularly in the developing nations. One- quarter of the global population may be affected
- Increased urbanization and improvement in living standards contributed to an increased exposure to a variety of indoor and outdoor pollutants and allergens, hence the raise in prevalence
- Most studies are based on data collection for seasonal AR. True prevalence of AR is being underestimated
- Large scale coordinated studies specifically designed to estimate the prevalence of AR in regions with different environmental factors and climates are needed

FACTORS INFLUENCING THE PREVALENCE OF AR

The prevalence of seasonal AR is higher in children and adolescents, while perennial AR seems to be more common in adults. In children, boys outnumber girls in terms of prevalence but tendency reverses in puberty and by adulthood, both sexes are being equally affected. This observed trend may be due to the female personality of self-reporting diseases or to a true impact of female sex hormones on disease development.

There is very little inter-racial variations implying that environmental factors seem have a greater influence than genetic differences. Increased urbanization and improvement in living standards especially in the developing regions have increased exposure to a variety of indoor and outdoor pollutants and allergens, all contributing to the increased prevalence. Climatic factors may directly affect the presenting symptoms or indirectly through allergens, sensitizing agents and population lifestyle.

PREVALENCE OF AR IN CHILDREN

The International Study of Asthma and Allergies in Childhood (ISAAC) program phases I, II and III held in more than 237 centers in 98 countries worldwide using standardized methodology, have demonstrated major worldwide variations for AR prevalence in children, with the lowest prevalence being observed mainly in centers from middle/low income countries, particularly in Africa/ Latin America. ISAAC phase III repeated the same questionnaire to assess the time trends 5-10 years after the initial phase I, and showed that the prevalence of AR is increasing in most of the areas with a few exceptions. Some of the highest increases were observed mainly in the non-Western region, particularly Asia-Pacific, as opposed to the western pop-

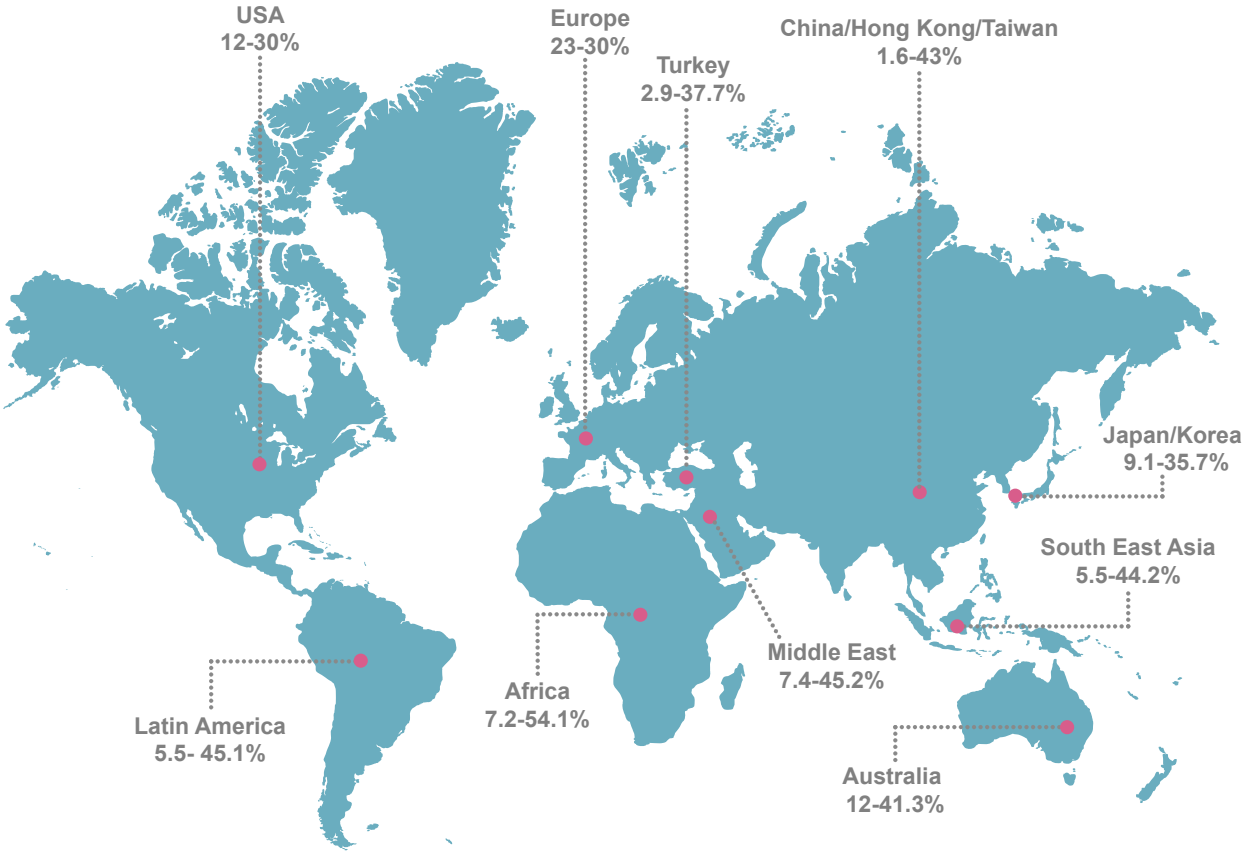

Figure 1 Prevalence of allergic rhinitis in different regions of the world, using ISAAC standardized methodology.

ulation like North America where AR prevalence tends to gradually decline.

PREVALENCE OF AR IN ADULTS

Global coordinated studies such as ISAAC in children are lacking. Population based cohort studies reported in Asia Pacific, Australia and Eastern Europe have demonstrated variations in prevalence of the AR in adults between the surveyed region. Self-administered, locally custom designed and European Community Respiratory Health Survey (ECRHS) questionnaires have been used, with variations ranging from 8.7-24.1% in China and 11.4-22.7% in Turkey.

Large scale studies specifically designed to estimate the prevalence of allergic rhinitis in regions with different climates are needed.

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2 NATURAL HISTORY OF ALLERGIC RHINITIS

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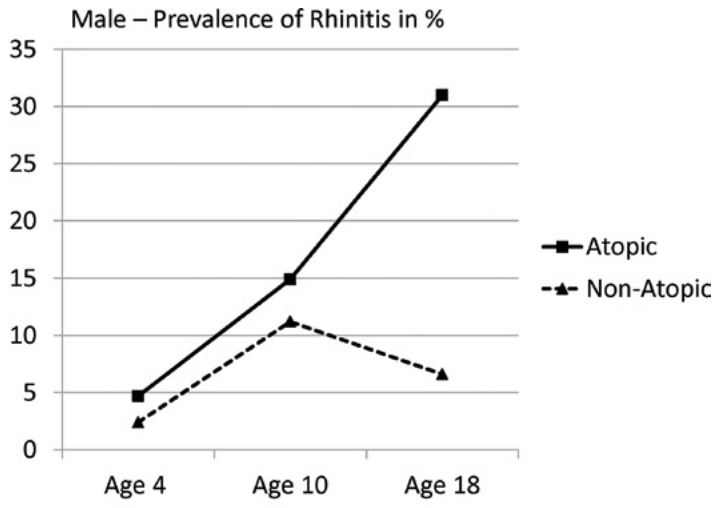
KEY MESSAGES

- Prevalence of rhinitis increases throughout childhood with a stronger association to male sex
- In pre-school years, rhinitis is primarily non-allergic and transient
- In boys, non-allergic rhinitis decreases in prevalence during adolescence, while in girls it increases consistently from 4 to 18 years, resulting in a female dominance of this condition in early adult life
- Gender and atopy are two major factors influencing the natural history of rhinitis

Allergy rhinitis (AR), with its' constellation of symptoms is a clinical diagnosis and hence reported prevalence and natural history varies widely. Cross-sectional studies across the globe, using standardized questionnaires, shows substantial average global prevalence of rhinitis, which increases from childhood (8.5% at 6-7 years) to 14.6% at 13-14 years. Keil et al, recently showed that prevalence of AR quadrupled from 6% at 3-years to 24% at 13-years in children with non-allergic parents and tripled from 13% to 44% for children with at least one allergic parent.. In the Isle of Wight Birth Cohort rhinitis prevalence increased 7-fold from 5.4% at 4-years to 35.8% at 18-years. This rise was seen in children of both allergic and non-allergic parents. There is very little information available regarding the course of AR through adult life. However, clinical experience and a few studies that have been done suggest that it takes a chronic course with significant remission and relapse.

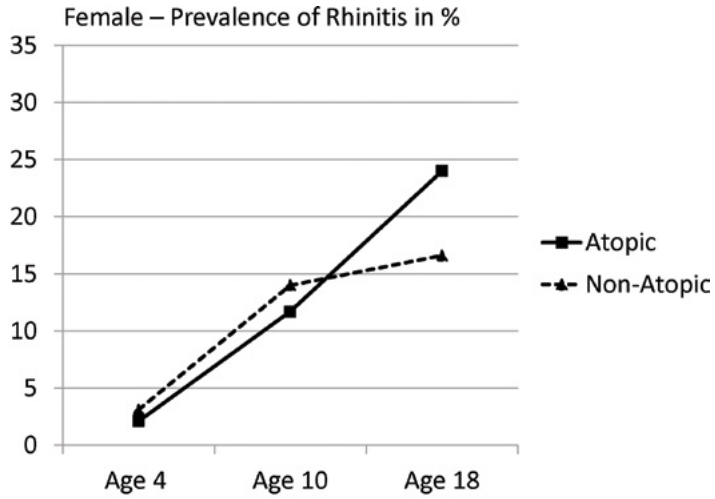
The classical "atopic march" portrays a characteristic evolution of allergic disease from one state to another through childhood, which typically suggested that rhinitis follows asthma, mostly appearing in later childhood or adolescence. However, it is likely that in reality, allergic diseases, especially asthma and rhinitis, exist together due to common underlying immune and epithelial dysregulation leading to airway inflammation and giving rise to the "one airway one disease" concept.

Atopy, as defined by positive skin test or presence of specific IgE, significantly influences the natural course of the disease. Rhinitis is conventionally regarded as an allergic disorder but similar constellation of symptoms can occur without evidence of allergic sensitization in the non-allergic rhinitis. There is a male preponderance in AR during childhood, which persists up to young adult life. Non-allergic rhinitis behaves differently. It is often transient during early childhood. It then increases in prevalence during later childhood with no clear sex dominance but acquired a female predominance by the age of 18-years as girls "grew into" it while boys "grew out of" rhinitis during adolescence. The different dynamic for allergic and non-allergic rhinitis in males and females is illustrated in Figures 1and 2. Similar gender switch during adolescence is seen in non-allergic asthma which is more common in boys but women acquire more non-allergic asthma during adolescence. Given the common underlying pathophysiology and adolescence period, it is



	n=493	n=516	n=407
Atopic:	4.7 (2.8-3.8)	14.9 (11.8-18.0)	31.0 (26.5-35.5)
Non-atopic:	2.4 (1.1-3.8)	11.2 (8.5-14.0)	6.6 (4.2-9.1)

Figure 1 Changes in Atopic and Non-atopic Rhinitis Prevalence for Boys over the First 18-years of Life. Figures indicate rhinitis prevalence (percentage with 95% confidence intervals) at each assessment for boys, stratified by atopic status. (*Adapted from Kurukulaaratchy RJ, Karmaus W, Raza A, et al. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. Clin Exp Allergy 2011;41:851-859.*)



	n=487	n=520	n=446
Atopic:	2.1 (0.8-3.3)	11.7 (9.0-14.5)	24.0 (20.0-28.0)
Non-atopic:	3.1 (1.5-4.6)	14.0 (11.1-17.0)	16.6 (13.15-20.05)

Figure 2 Changes in Atopic and Non-atopic Rhinitis Prevalence for Girls over the First 18-years of Life. Figures indicate rhinitis prevalence (percentage with 95% confidence intervals) at each assessment for girls, stratified by atopic status. (*Adapted from Kurukulaaratchy RJ, Karmaus W, Raza A, et al. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. Clin Exp Allergy 2011;41:851-859.*)

plausible that factors such as sex, puberty/ hormones and obesity influence the natural course of both asthma and rhinitis.

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3 BIRTH COHORTS STUDIES IN ALLERGIC RHINITIS

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KEY MESSAGES

- Several birth cohorts studied the natural course of allergic rhinitis (AR) and showed a steep increase in the prevalence and the severity of AR
- The direct relation with atopy as part of the "allergic march" is confirmed by most but not by all studies
- Birth cohort studies also evaluated the imapct of genetic variants and of the effect modifiers, such as pollution
- Molecular diagnosis in the preclinical phase of the AR could provide a window of opportunity for primary prevention

Several birth cohorts studied the natural course of atopic diseases. Especially for asthma, allergic rhinitis (AR), eczema and sensitisation to inhalant and food allergens we have European data on approximately 20.000 children. Common data analyses were performed as meta analyses or pooled analyses. There are certain limitations as different cohort studies have slightly different designs, however, many of them used the same validated questionaires (ISAAC) and performed similar assays for the determination of specific serum IgE. Thus they appear to be comparable in an acceptable way.

In the Multicentre Allergy Study MAS-90 ARIA criteria were used to define rhinitis in children and young adults. Symptoms were defined as "severe" (impairment of daily activities) or "mild" (no impairment), "persistent" (duration >1 month) or "intermittent" (≤1 month) using annual questionnaires. The 12-months prevalence of AR quadrupled from 6% (at age 3y) to 24% (at age 13y) in children with non-allergic parents, and more than tripled from 13% (3y) to 44% (13y) in children with at least 1 allergic parent (figure 1). Boys were more frequently affected than girls (figure 2). Half or more of the children with AR had "severe persistent" symptoms. At age 13, these children were significantly more often sensitized than those with "mild persistent" disease: 91% vs. 70% (p=0.015). Sensitization to aero-allergens (adjusted OR 18.9; 95%CI 9.3-38.4), and having 2 allergic parents (3.1; 1.1-9.3) were significantly associated with AR. According to the ARIA criteria, the impact of AR seems to be substantial; the vast majority of affected children suffered persistently for periods of 2 months or more annually, and most of the children with persistent AR were impaired in their daily activities. At 7 years of age, seasonal allergic rhinitis (SAR) developed in 15% of the children. Children with SAR already in the second year of life were all born in spring or early summer. Risk factors for SAR were male sex, atopic parents having SAR themselves, first-born child, early sensitization to food and atopic dermatitis.

The Follow-up of the German MAS at 20 years of age showed that rhinitis was still the most frequent outcome observed. 290 individuals developed 'allergic rhinitis' within 13,179 person years observed. The risk to develop AR was higher with parents' history of AR (adjusted hazard ratio [95% confidence interval]: 2.52 [1.94; 3.27]), urticaria (1.32 [1.00;1.74]) or asthma (1.29 [0.95;1.75]). Early allergic sensitization (4.50 [3.30;6.13]), eczema within the first three years (1.88 [1.43;2.48]),

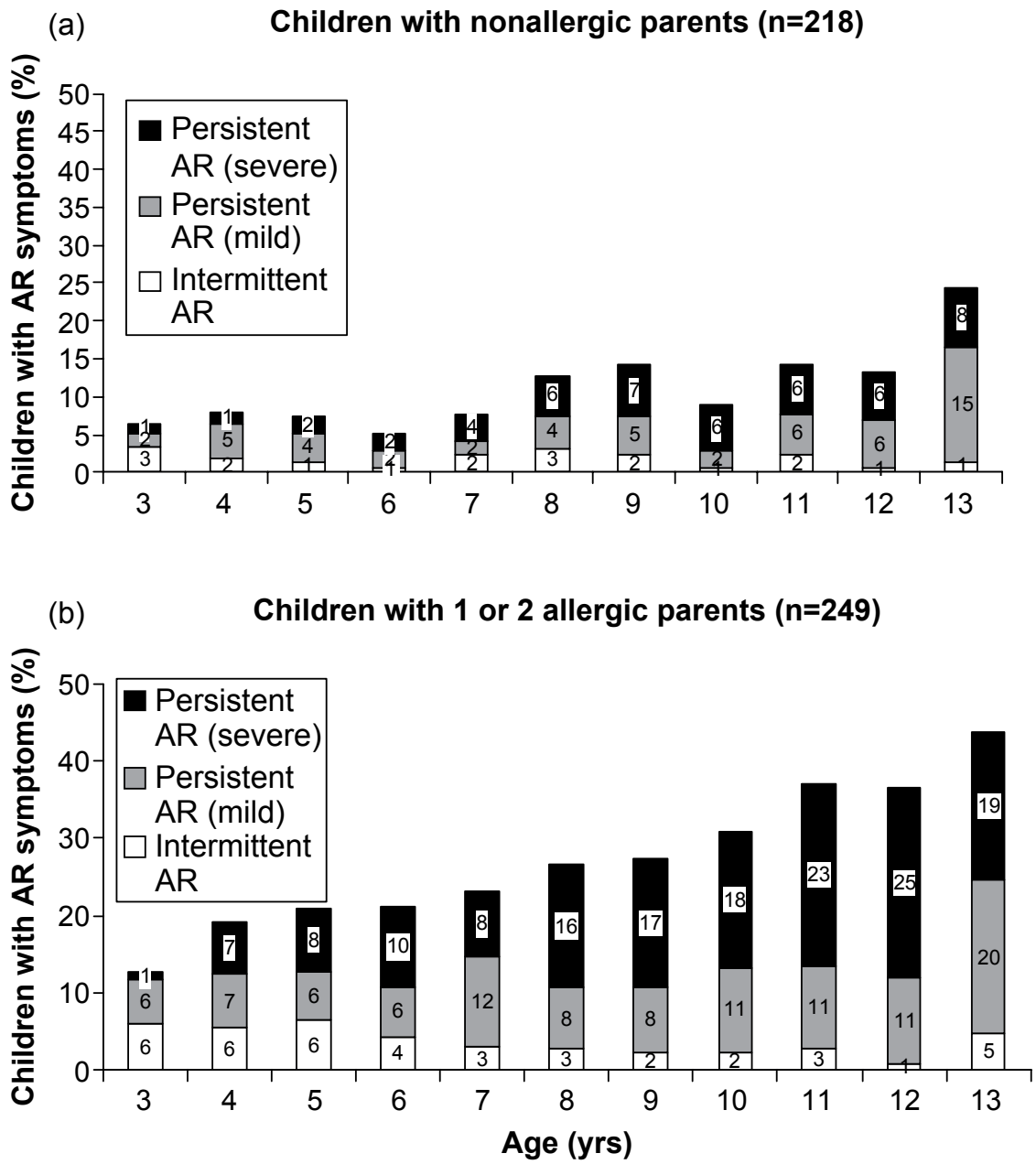

Figure 1 Heredity and prevalence of allergic rhinitis symptoms in the German MAS. (*Reproduced from Keil T, Bockelbrink A, Reich A, et al. The natural history of allergic rhinitis in childhood. Pediatr Allergy Immunol 2010;21:962-969, with permission from Wiley-Blackwell.*)

male sex (1.28 [1.01;1.61]) and birthday in summer or autumn (1.26 [1.00;1.59]) were independent predictors of AR up to age 20. The secondary outcome 'AR and asthma' was linked to several modifiable risk factors (smoking in pregnancy; starting day-care before age 18 months, or after age 36 months). Receiving recommended vaccinations was associated with lower incidence of rhinitis combined with current asthma.

In the Swedish BAMSE study 13.8% of the participating children had AR, while 6.4% had non-allergic rhinitis at age 8 years, while at age 4 years, 5% had AR and 8% had non-allergic rhinitis. Remission was much higher for

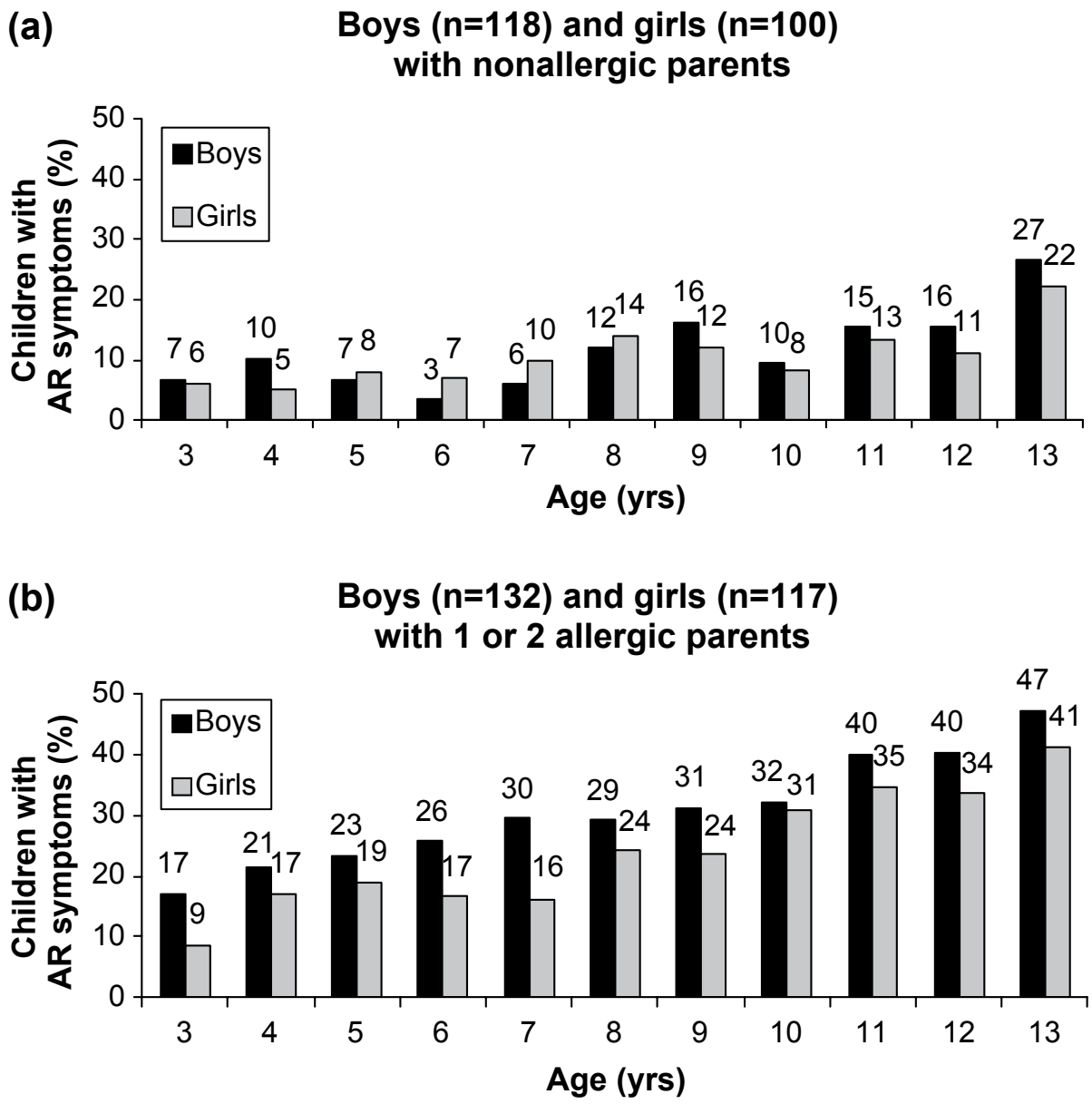

Figure 2 Influence of gender and heredity for the prevalence of allergic rhinitis in the German MAS. (*Reproduced from Keil T, Bockelbrink A, Reich A, et al. The natural history of allergic rhinitis in childhood. Pediatr Allergy Immunol 2010;21:962-969, with permission from Wiley-Blackwell.*)

non-allergic rhinitis than for AR (73% versus 12%). Of the sensitized 4-year-old individuals without rhinitis, 56% had developed AR at age 8 years. Parental hay fever increased the odds of AR in offsprings (OR 2.2; 95% CI 1.6-3.2), whereas isolated parental eczema or asthma did not. The odds for non-allergic rhinitis increased when one parent had two or more allergy-related diseases.

In the Isle of Wight cohort, overall rhinitis prevalence increased from 5.4% at age 4 years to 35.% at 18 years ($p<0.001$), without gender difference. AR prevalence increased steadily from 3.4%

at 4 years to 27.3% at 18 years (p<0.001). AR was commoner in boys at 18 years (p=0.02) and associated with greater positive transition in boys from 10 to 18 years (p=0.01). Prevalence of non-atopic rhinitis also increased from 4 to 18 years (p=0.003) and was greater in girls at 18 years (p<0.001) reflecting higher female positive transition from 10-18 years (p<0.001). Non-atopic rhinitis remission was highest in early life and reduced in later childhood/adolescence.

In the Norwegian Environment and Childhood Asthma Study current rhinitis was reported in 254 of 1019 children (25%) at age 10 years. Children with rhinitis and allergic sensitization had more frequently bronchial hyperreactivity.

IS ALLERGIC RHINITIS PART OF THE ATOPIC MARCH?

In European birth cohort studies AR is found in 10-25% of children and adolescents depending on the recruitment area. While in some cohorts it appears that early atopic eczema and early sensitisation to foods and inhalant allergens appears to be a risk factor for later airway disease, other cohorts have reported a heterogeneous developmental profile for eczema, wheeze and rhinitis. In the British ALSPAC and MAAS cohorts, applying Bayesian machine learning methods in order to identify distinct latent classes only 7% of children were found to follow trajectory profiles resembling the atopic march.

An analysis of 12 ongoing European birth cohort studies participating in MeDALL (Mechanisms in the Development of ALLergy) included over 16.000 children aged 4 years and 11080 aged 8 years. Comorbidity of eczema, rhinitis and asthma was investigated and defined as coexistence of two or three diseases in the same child. 1.6% of children were found to have comorbidity at age 4 years and 2.2% of the children at age 8 years. Strikingly, IgE sensitisation was not the dominant causal mechanism of comorbidity.

In a Swedish publication, 32.7% of children with mild eczema and 45% of children with moderate-to-severe eczema showed also rhinitis, favouring the conclusion, that severity of eczema is associated with rhinitis and allergic airway disease. Furthermore, at age 12 years, 7.5% of the children in the BAMSE cohort were affected by at least two allergy-related diseases.

In the German MAS AR until the age of 5 years was found to be a predictor for developing wheezing between the ages of 5 and 13 years, with an adjusted relative risk of 3.82 (p<0.001). This association was not attributable to the type of sensitization, the severity of sensitization, or atopic dermatitis during the first 2 years of life. In this group of children, 41.5% of all new cases of wheezing occurred among children with preceding AR (figure 3).

ALLERGIC RHINITIS AND OTITIS MEDIA

In the Danish COPSAC birth cohort (Copenhagen Prospective Studies on Asthma in Childhood) 291 children in the 6th year of life were evaluated for asthma, allergic and non-allergic rhinitis, eczema and also for otitis media with effusion. Otitis media with effusion was diagnosed in 39% of the cohort and this was associated with AR (aOR 3.36; CI 1.26-8.96; p=0.02) but not with non-allergic rhinitis, asthma or eczema.

GENETIC VARIANTS AND EFFECT MODIFICATION

Filaggrin gene variants are associated with severer atopic eczema and skin barrier dysfunction, with asthma and poor lung function at school age and in some studies also with rhinitis. In the Isle of Wight study, filaggrin gene variants increased the risk of asthma (RR 1.3; 95% CI 1.06-1.80) and rhinitis (RR 1.37; 95% CI 1.16-1.63). While eczema and allergic sensitisation modulated and increased the risk for asthma, this could not be shown for rhinitis. This supports the interpretation, that rhinitis and asthma in childhood and adolescence do not necessarily follow a common pathway in the group of children carrying the filaggrin mutations.

In another pooled analyses certain single nucleotide polymorphisms within the TLR4 and TNF genes increased the risk of AR in children. Traffic related air pollution was not a relevant effect modifier.

MOLECULAR SPREADING IN THE PRECLINICAL PHASE OF AR

The development of AR seems to be determined by the development of specific sensitization. In the case of grass pollen sensitization in the German MAS, an initial IgE response to an initiator molecule, in > 75% of cases Phl p1 in a preclinical phase, precedes a more complex sensitization to several molecules: Phl p 4, Phl p 5, Phl p 2, Phl p 6 and Phl p 11 and later Phl p 12 and Phl p 7. Sensitization at age 3 predicted SAR by age 12 years (PPV 68%; 95% CI, 80-87%). At this early preclinical prediction time, the number of recognized molecules and the serum levels of IgE to *Phleum pratense* were significantly lower than at 3 or more years after the clinical onset of

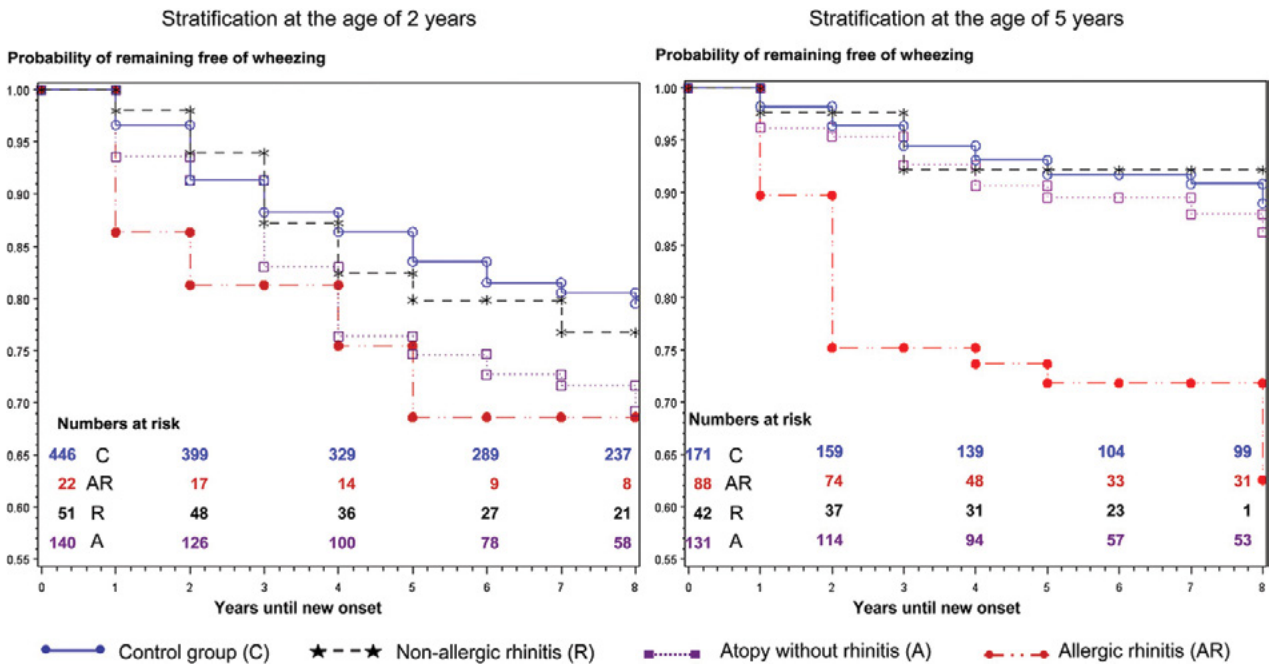

Figure 3 The risk of wheezing is determined by preceding allergic rhinitis in the German MAS. (*Reprinted from J Allergy Clin Immunol, 126/6, Rochat MK, Illi S, Ege MJ, Lau S, Keil T, Wahn U, von Mutius E; Multicentre Allergy Study (MAS) group. Allergic rhinitis as a predictor for wheezing onset in school-aged children, 1170-1175.e2, Copyright 2010, with permission from Elsevier.*)

SAR and could thus be a potential window of opportunity for preventive early intervention.

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4 GENOME-WIDE ASSOCIATION STUDIES IN ALLERGIC RHINITIS

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KEY MESSAGES

- Only 4 genome-wide association studies (GWAS) studies of allergic rhinitis have been performed
- Genes for mitochondrial function, B cells and regulatory T cells have been identified
- The next steps are further integrative omics studies of AR using GWAS, gene expression, microRNA, and metabolomics

Genome-wide association studies (GWAS) utilize the natural correlation of single nucleotide polymorphisms (SNPs) with one another to allow genotyping of a reduced subset of SNPs across the genome. These SNPs are then associated with the phenotype of allergic rhinitis (AR) in either a family-based or a case control study design.

AR is an IgE-mediated inflammatory disease of the nasal mucosa. It can occur with or without asthma or eczema, the two other primary allergic conditions. Relatively few GWAS studies have been reported in AR. The initial paper documented **MRPL4** (Mitochondrial ribosomal protein L4, chr 19p13.2) and **BCAP** (B-cell adaptor for phosphatidylinositol 3 Kinase, Chr10q24.1) as having suggestive associations without genome-wide significance. A large European study then identified one genome-wide significant locus for AR: chromosome 11 open reading frame 30 (**C11orf30**). A meta-analysis of genome-wide associations with self-reported cat, dust-mite, and pollen allergies among Europeans identified 16 shared susceptibility loci, including 8 previously associated with asthma. Most recently, a North American integrative genomics study (figure 1) utilizing both GWAS and gene expression identified a locus near transcription factor FER3-Like (**FERDL3**) on chromosome 7p21.1 as a genome-wide significant AR susceptibility locus across ethnic groups, in addition to four genome-wide significant loci among Latinos specifically. The integrative analysis with gene expression data implicated a gene module enriched for mitochondrial pathway genes (figure 2). Although other studies have examined AR and asthma or AR and atopic dermatitis, these 4 studies are the only ones that focus exclusively on AR as a disease. Methodologically these studies seem sound in that they have some form of replication, are of large sample size, and all have addressed the major validity threat of population stratification.

The existing literature supports the involvement of mitochondrial genes, genes related to B cells and epithelial barrier function and regulatory T cell function as being of prime importance in AR. Future directions will need to go in the direction of the recently published integrative genomics paper where gene expression and GWAS data were integrated in one analysis and a systems genomics approach using pathway models was implemented. This methodology holds great promise in helping to determine the underlying pathobiology of AR. One of the positive advantages that are available in AR is that investigators can obtain nasal cells from lavage or biopsy and use these cells to perform multi Omic studies including metabolomics and microRNA studies.

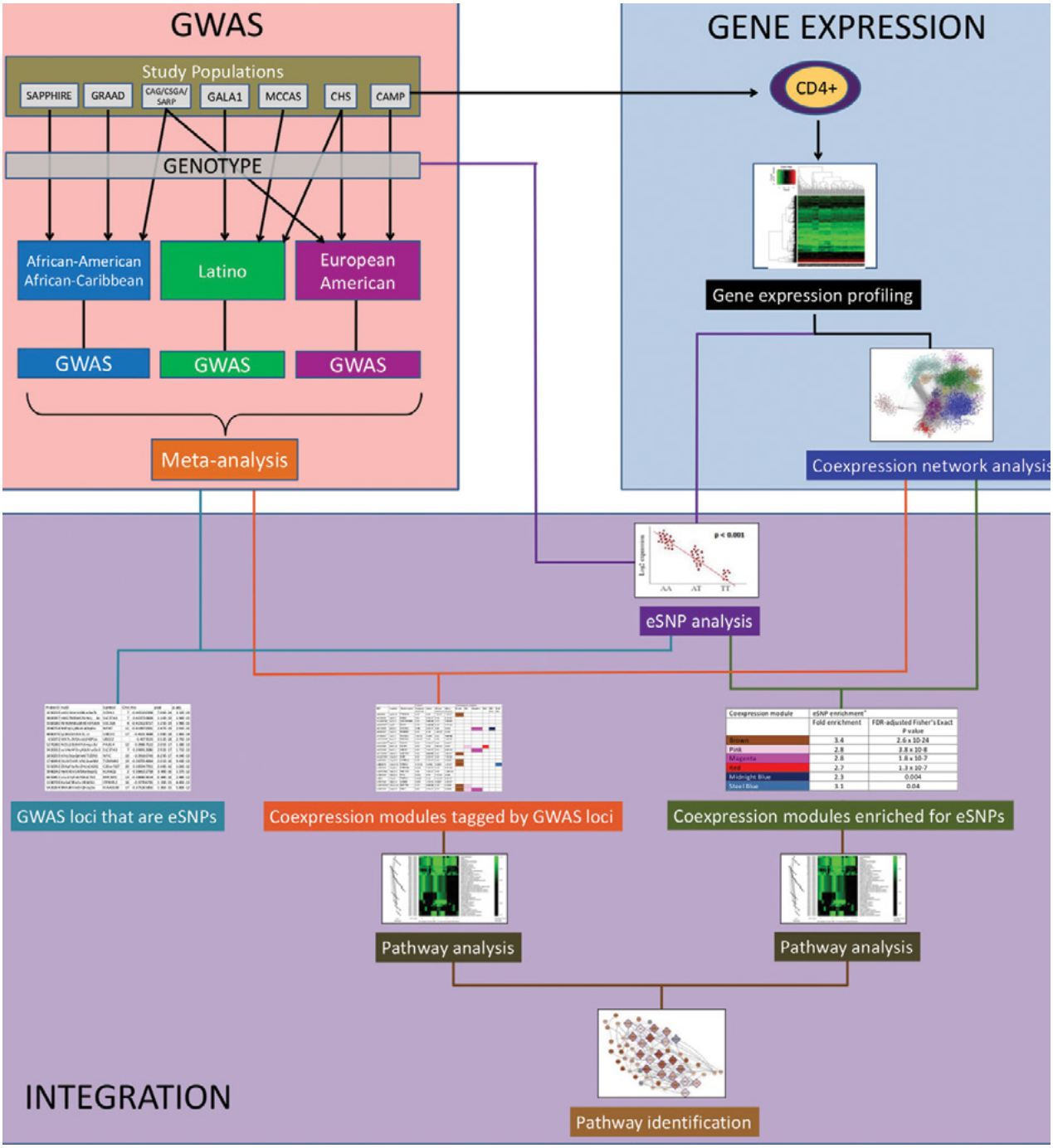

Figure 1 Study flow for the integrated genome-wide association, coexpression network, and expression single nucleotide polymorphism analysis of allergic rhinitis. CHS = Children's Health Study, CAMP = Childhood Asthma Management Program, CAG = Chicago Asthma Genetics Study, CSGA = Collaborative Studies on the Genetics of Asthma, SARP = Severe Asthma Research Program, GALA1 = Genetics of Asthma in Latinos, MCCAS = Mexico City Childhood Asthma Study, GRAAD = Genomic Research on Asthma in the African Diaspora and Barbados, SAPPHIRE = Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity. (*From Bunyavanich S, Schadt EE, Himes BE, Lasky-Su J, Qiu W, Lazarus R, et al. Integrated genome-wide association, coexpression network, and expression single nucleotide polymorphism analysis identifies novel pathway in allergic rhinitis. BMC Med Genomics 2014;7:48.*)

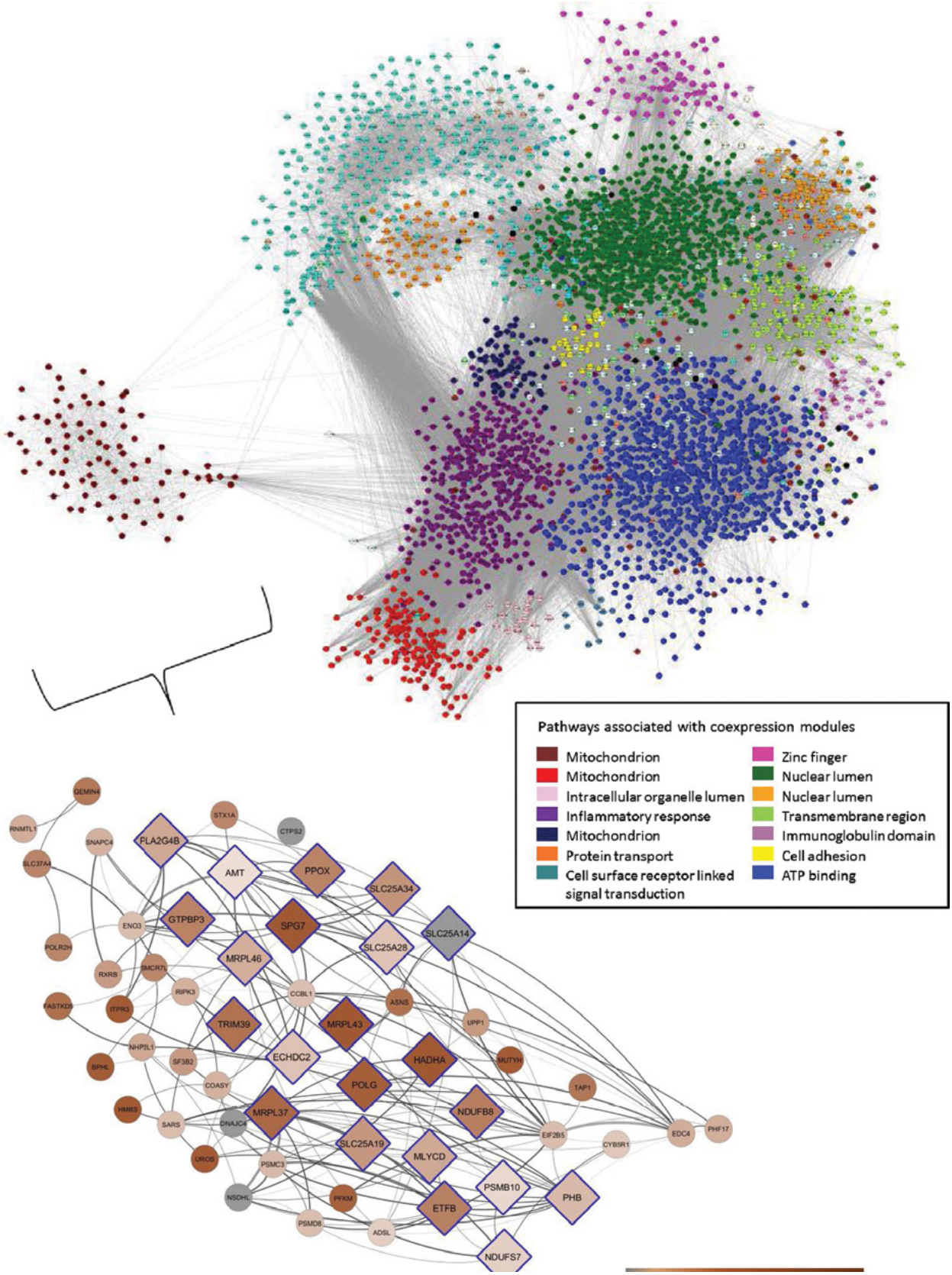
Pathways associated with coexpression modules
Mitochondrion
Mitochondrion
Intracellular organelle lumen
Inflammatory response
Mitochondrion
Protein transport
Cell surface receptor linked signal transduction
Zinc finger
Nuclear lumen
Nuclear lumen
Transmembrane region
Immunoglobulin domain
Cell adhesion
ATP binding
GEMIN4
RNMTL1
SNAPC4
PLA2G4B
STX1A
CTPS2
SLC37A4
AMT
PPOX
SLC25A34
GTPBP3
SPG7
SLC25A14
ENO3
SLC25A28
POLR2H
MRPL46
RXRB
SMCR7L
RIPK3
CCBL1
ASNS
FASTKD3
ITPR3
TRIM39
MRPL43
UPP1
NHP2L1
ECHDC2
HADHA
MUTYH
BPHL
SF3B2
COASY
POLG
TAP1
HMBS
SARS
DNAJC4
MRPL37
NDUFB8
EIF2B5
EDC4
PHF17
SLC25A19
CYB5R1
UROS
MLYCD
PSMC3
PSMB10
NSDHL
PFKM
PHB
ETFB
PSMD8
ADSL
NDUFS7

Figure 2 $CD4^+$ lymphocyte coexpression network with detail of the brown coexpression module. A. Each circle represents a gene. Weighted gene coexpression analysis identified groups of genes with similar patterns of gene expression and interconnectivity (coexpression modules). The 41 coexpression modules identified are labeled by color. Pathways associated with the largest coexpression modules are denoted in the legend. B. Interconnectivity of the brown coexpression module is shown in detail. Tagged by 6 allergic rhinitis GWAS loci, this coexpression module was highly enriched for allergic rhinitis-associated eSNPs (3.4-fold enrichment, FDR-adjusted P value = 2.6 × 10−24) and also highly enriched for pathways related to mitochondrial function (8.6-fold enrichment, FDR-adjusted P value = 4.5 × 10−72). Genes containing allergic rhinitis-associated eSNPs are marked in brown, with those containing eSNPs with lowest P-value for association between genotype and gene expression marked with greatest brown saturation. Genes in pathways related to mitochondrial function are marked by diamonds with blue outline. Higher correlation between gene expression is shown with thicker and darker edges. (*From Bunyavanich S, Schadt EE, Himes BE, Lasky-Su J, Qiu W, Lazarus R, et al. Integrated genome-wide association, coexpression network, and expression single nucleotide polymorphism analysis identifies novel pathway in allergic rhinitis. BMC Med Genomics 2014;7:48.*)

It is quite likely that the next steps here are further integrative Omics studies of AR using GWAS, gene expression, microRNA, and metabolomics. If these studies are performed on subjects before and after allergen exposure using the subject as his or her own control, it is likely that even a small sample size will yield positive results and further refine the biology of the disease.

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5 EPIGENETIC MECHANISMS IN ALLERGIC RHINITIS

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KEY MESSAGES

- Genetics alone cannot explain the increasing prevalence of allergic rhinitis (AR)
- Epigenetics is likely to be involved in the pathology of AR
- DNA methylation patterns differ between patients and healthy individuals, and between patients before and after allergen immunotherapy
- DNA methylation may be a useful predictive marker and therapeutic target in AR

The modest effects of genetic variants and increasing prevalence of common diseases like asthma and seasonal allergic rhinitis (SAR) suggest the pathogenic importance of environmental factors and the involvement of epigenetic mechanisms. Epigenetic mechanisms include DNA methylation, which in general inhibits mRNA expression and modifications of chromatin structure, such as histone proteins, which may either deny or facilitate binding of transcription factors to promoter regions. Several studies have shown the importance of DNA methylation in T-cell differentiation as well as indifferent T-cell subsets from asthmatic patients, as recently reviewed.

SAR is an excellent model to study such mechanisms, because the main environmental trigger, pollen, is known and the effects of allergen exposure can be studied *in vitro* by allergen challenge of peripheral blood mononuclear cells (PBMCs) from patients outside of the season. Moreover, changes during tolerance induction by allergen immunotherapy (3) can also be studied. However, there are relatively few studies of epigenetic mechanisms in SAR. One recent study suggests that the beneficial effects of AIT may be due to in part to reduced DNA methylation of the *FoxP3* promoter region in T regulatory cells. Several studies in mouse models of SAR have also observed changes in DNA methylation as key regulatory of genes expression in $CD4^+$ T-cells (Figure 1).

To identify changes in DNA methylation in SAR patients, we generated genome-wide DNA methylation and gene expression profiles of *ex vivo* $CD4^+$ T-cells from SAR patients and healthy controls. DNA methylation profiles clearly separated SAR patients from controls, during and outside the pollen season. Moreover, a significant correlation between symptom scores and DNA methylation was found. Conversely, gene expression profiles of the same samples failed to separate patients and controls. Separation by methylation but not by gene expression was also observed in an *in vitro* model system in which purified PBMCs from patients and healthy controls were challenged with allergen. These findings highlight the potential of DNA methylation as a biomarker useful for the stratification of SAR. DNA methylation has also diagnostic potential, since it's more stable and easy to measure than mRNA and perhaps proteins.

Finally, unlike genetic changes, epigenetic enzyme activity and epigenetic profiles are readily altered by several approved drugs and nutrients, such as vitamins C or D. Thus, epigenetic alterations in immune disease may not only

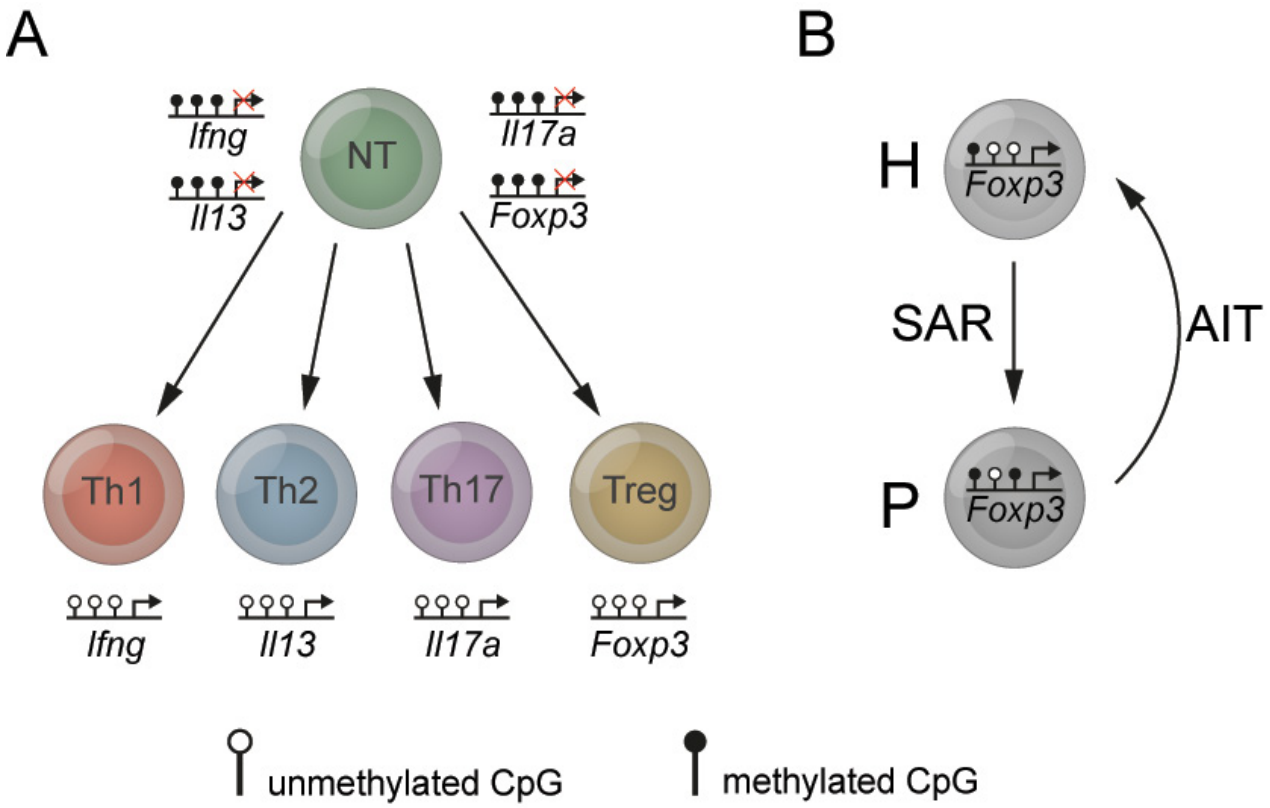

Figure 1 DNA methylation dynamics in CD4⁺ T-cells. (A) Several key loci undergo loss of promoter DNA methylation during CD4⁺ T-cell differentiation. Naïve CD4⁺ T-cells (NTs) can be differentiated *in vitro* into several T effector (T-helper type 1, type 2, and type 17) and T regulatory (Treg) cell types; an *in vitro* polarisation assay. Changes in locus specific or genome-wide methylation can then be assessed during this process. (B) Increased promoter DNA methylation in allergic rhinitis patients are partially reversed after allergen immunotherapy (AIT). SAR = seasonal allergic rhinitis.

serve as predictive markers, but also as potential targets for novel epigenetic-taregeted therapies.

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6 FROM GENE EXPRESSION MEASUREMENTS TO EPIDEMIOLOGIC STUDIES

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KEY MESSAGES

- Measuring gene expression, RNA stability and quality require special attention
- Expression of pattern-recognition receptors and regulatory cytokines might play a role in the immunological mechanisms of the hygiene hypothesis
- Gene- environment interaction deserves particular attention in the context of the epidemic rise of allergic diseases
- Gene expression measurements in the context of epidemiological studies are a useful tool to reproduce in humans the findings from cell cultures and from mouse models

MEASURING GENE EXPRESSION

Gene expression measurements became an attractive tool to assess biological responses in epidemiological studies, as they might reflect both genetic and environmental influences. However, collection of blood samples for gene expression assessment poses various technical pitfalls. Collecting blood samples into tubes containing an RNA-stabilizing solution increases RNA yield and reduces its variability. Long-term storage of samples may lead to RNA degradation, requiring special attention in longitudinal studies.

THE HYGIENE HYPOTHESIS AND GENE EXPRESSION

In epidemiological studies, immunological mechanisms underpinning the hygiene hypothesis have been extensively studied using gene expression (Figure 1). The hygiene hypothesis states that environmental exposures to high levels of microbial components, such as occurring in the traditional farming setting, are one of the major preventive factors for the development of allergic diseases, such as allergic rhinitis (AR) and or for the sensitization to inhalant allergens. In fact such environments up-regulate the expression of pattern-recognition receptor genes such as Toll-like receptors (TLR) and the expression of genes of their signaling cascade. Furthermore, the gene expression of regulatory cytokines such as IL-10 and TGF-β in blood leukocytes is strongly induced among farmers' children (Figure 2).

There are evidences that the protective effect of farm exposures against the occurrence of allergic diseases could already be effective during pregnancy. Exposure of pregnant mothers to farm stables is associated with an increase of gene expression of receptors of the innate immunity, TLR2, TLR4 and CD14 (Figure 2). Results from a birth cohort show that an increased gene expression of innate immunity receptors at birth is protective against the development of atopic dermatitis.

CHRONIC RHINOSINUSITIS AND GENE EXPRESSION

Evidence for a defective barrier function is shown in patients with chronic rhinosinusitis (CRS). Biopsies of patients with CRS have a decreased gene expression of tight junction (TJ) genes occludin and zonula occludens 1 that is associated with a disruption of the epithelial integrity. The relative importance of primary (genetic) vs secondary (inflammatory) changes in TJ gene expression needs further study.

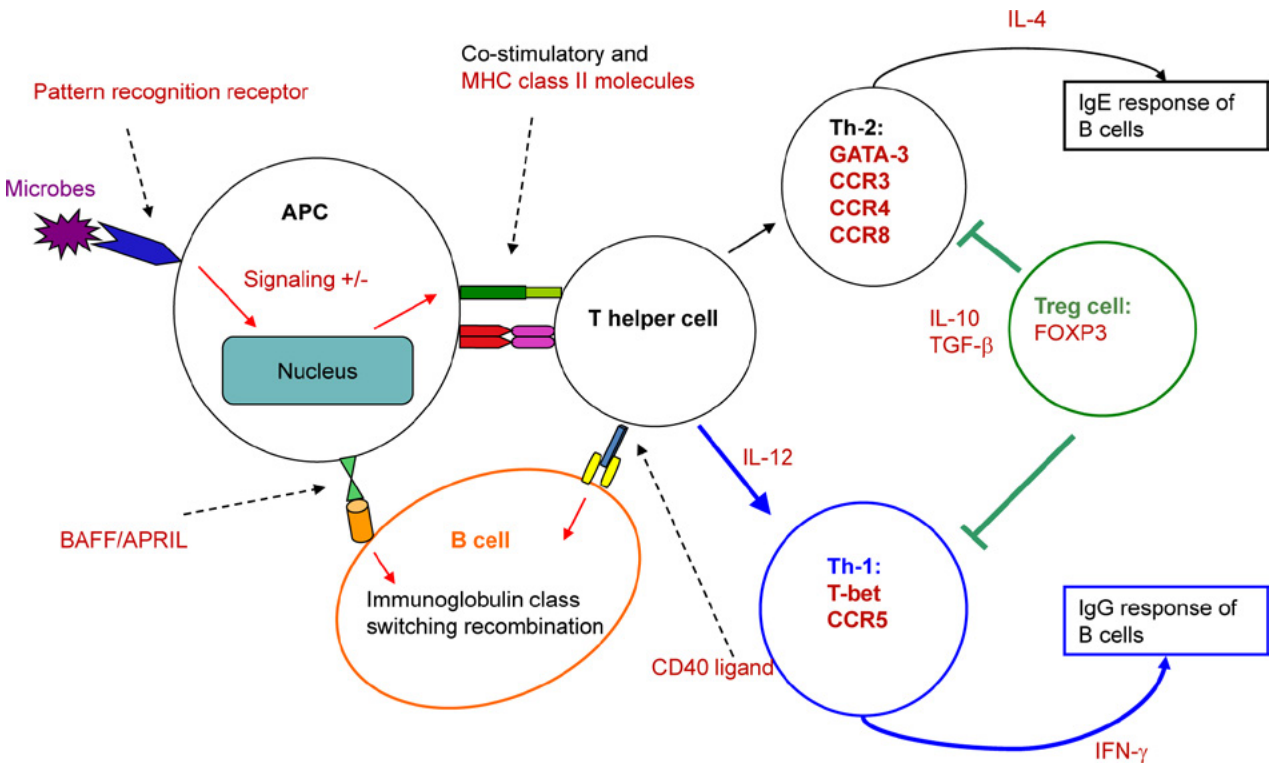

Figure 1 T helper cell differentiation and B cell activation by the innate immune system. Schematic overview showing how microbes activate the innate immune system leading to T helper cell differentiation and proliferation and how immunoglobulin class switching recombination is induced via a T helper cell-dependent and independent pathway. In red, genes whose expression levels have been intensively studied in the context of epidemiological studies. APC, antigen-presenting cell; red, gene expression of these marker molecules was measured in this study. Abbreviations: APC = antigen presenting cell; APRIL = a proliferation inducing ligand; BAFF= B cell activating factor; CCR = CC-chemokine receptor; IL= interleukin; TGF=transforming growth factor; Th = T helper cell. (*From Frei R, Roduit C, Bieli C, Loeliger S, Waser M, Scheynius A, et al. Expression of genes related to anti-inflammatory pathways are modified among farmers' children. PLoS One 2014;9:e91097.*)

GENE-ENVIRONMENT INTERACTION

The levels of expression of certain genes are not influenced by environmental exposures alone, but they depend also on the type of alleles interacting with the environment. As shown by farm studies raw milk consumption is associated with increased expression of the CD14 gene only if a certain polymorphism of the CD14 gene is present.

CONCLUSION

Gene expression measurements in the context of epidemiological studies are a useful tool to reproduce in humans the findings from cell cultures and mouse models. The availability of new technologies such as RNA sequencing will boost the findings in this research area.

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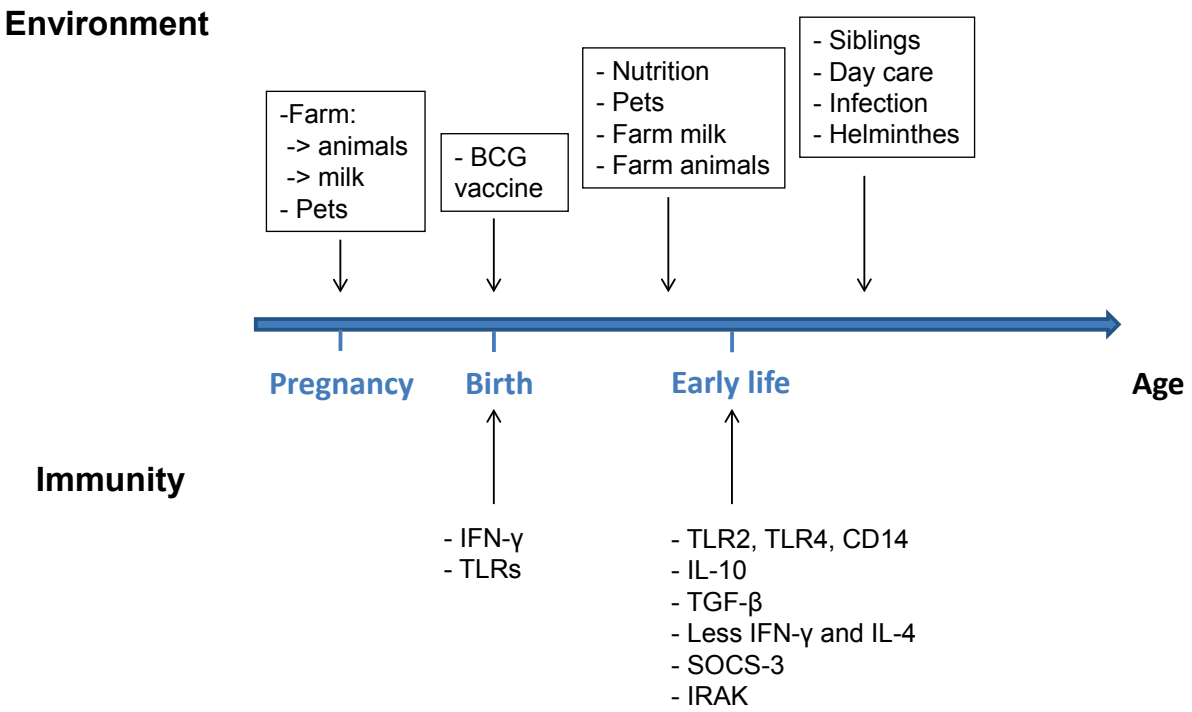

Figure 2 Overview of environmental factors reducing the risk of developing allergies in children over time and the associated immunological mechanisms described by gene expression measurements. Abbreviations for figure 2: IFN=interferon; IL= interleukin; IRAK = IL1 receptor-associated kinase; SOCS = suppressor of cytokine signaling proteins; TLR=Toll-like receptor; TGF = transforming growth factor

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7 PERINATAL INFLUENCES ON THE DEVELOPMENT OF ALLERGIC RHINITIS

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KEY MESSAGES

- Parental atopy, genetics and epigenetics influence development of allergic rhinitis (AR) in childhood
- Early life exposure to a farming environment protects against development of atopic diseases including AR later in life
- Microbial and nutritional diversity are associated with a lower risk of developing AR.

DEVELOPMENT OF ALLERGIC RHINITIS IN CHILDHOOD

Allergic rhinitis (AR), one of the most common allergic diseases in childhood, shows a shift of onset to younger ages with further increasing prevalence until adolescence. AR has an impact on quality of life, performance at school/work and socioeconomic burden. The onset of this IgE-mediated disease in children usually succeeds the development of atopic dermatitis (AD) and childhood asthma, being often related to one or both. Different phenotypes were described differentiating between local and systemic AR.

EARLY LIFE DETERMINANTS OF ALLERGIC RHINITIS

While several studies have shown that perinatal influences alter immune regulation early in life and subsequent development of allergic diseases such as childhood asthma, studies on early life mechanisms for AR alone are rare. This is due to its interrelation with AD and asthma, to partly shared mechanisms, and to its' later onset mostly succeeding AD and asthma. A variety of underlying factors are relevant during a perinatal "window", where disease development may be originated with symptoms succeeding later in life. In the following, primarily studies on early life determinants of AR are included (Figure 1).

Role of family history, infections and environmental exposure for AR development

A family history of atopy is a known risk factor for AR development. In two German studies (Multicenter Allergy cohort with 820 children, PAULA study with 526 children), parental hay fever or maternal atopy, infections, and bacterial exposure, respectively, were related to higher risk of AR in the offspring, importantly before the onset of symptoms, potentially acting as immunomodulators enhancing or inhibiting the development of AR. Farm exposure early in life protecting from AR is certainly one of the strongest factors shown repetitively, similar to asthma prevention.

Recent studies on the microbiome indicate that reduced bacterial diversity of the infants' intestinal flora was associated with increased risk of AR, but not with asthma or AD.

Genetics and epigenetics in the development of AR

Genetics are partially important in AR development, however not necessarily sharing the same susceptibility loci. Despite the high prevalence of AR, only three GWASs of AR have been reported identifying key genes such as MRPL4, BCAP, C11orf30/LRRC32 and FERD3L (Table 1). C11orf30/LRRC32 was relevant in GWAS for AR, asthma and AD. While overlapping loci may indicate a progression of allergic diseases from childhood AD to AR and asthma ("atopic march), a close relationship between AR and

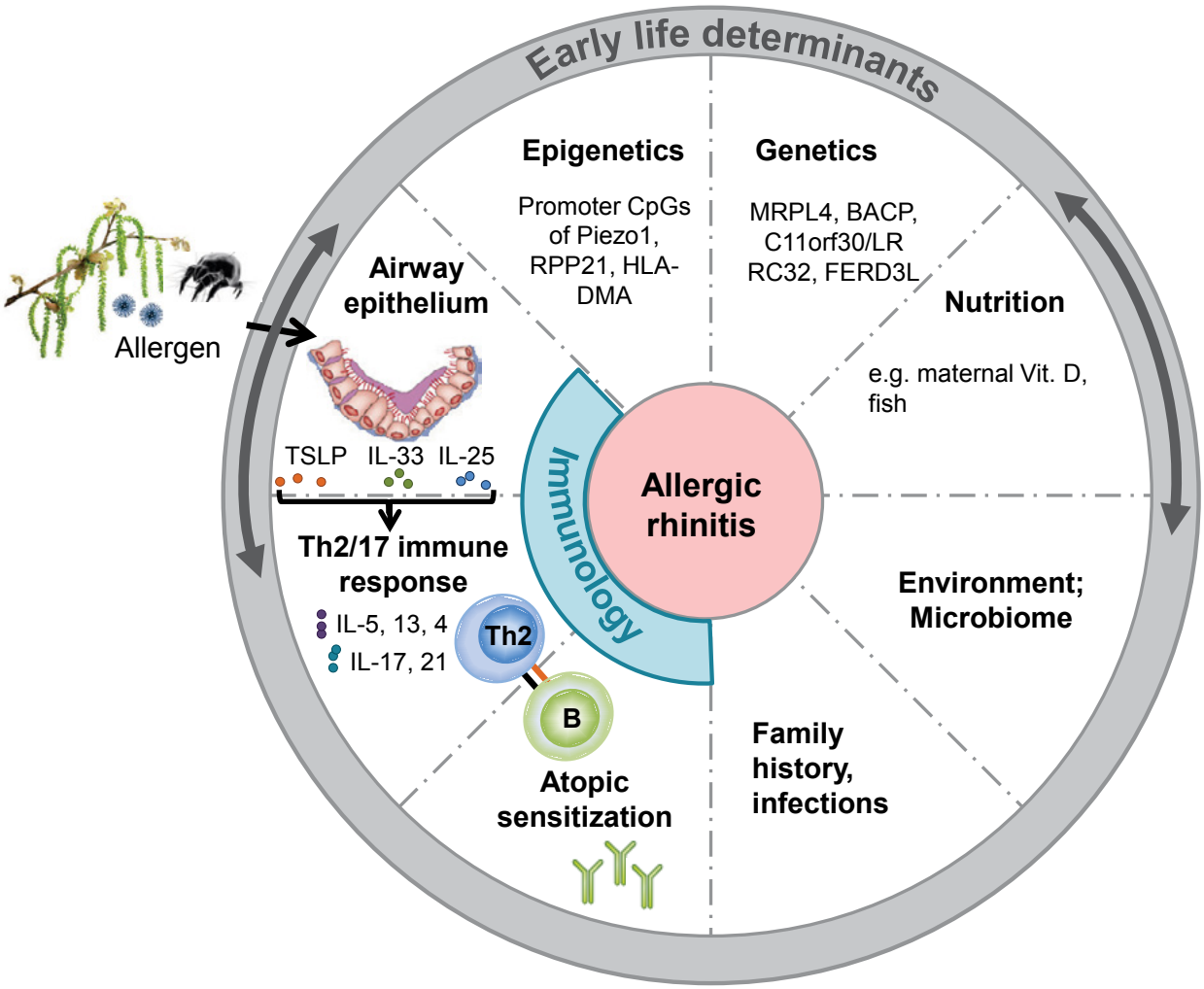

Figure 1 Early life determinants of AR. (*Adapted from Raedler D, Schaub B. Immune mechanisms and development of childhood asthma. The Lancet Respiratory medicine. 2014;2(8):647-56.*)

asthma may indicate the concept of „united airways" from early life onwards. Certainly, epigenetic effects, gene–gene interactions and gene–environment interactions have to be investigated in future genetic studies on AR.

Epigenetics, namely acquired and potentially reversible modifications that do not include alterations in the primary DNA sequence, comprise regulation via DNA methylation, histone modification, and non-coding RNAs and are likely to contribute to the environmental origins of asthma and its phenotypic variability. For AR alone, very few studies have been reported, with one differentiating AR vs controls by epigenetics focusing on promoter CpGs of PIEZO1, RPP21 and HLA-DMA.

Early life nutrition and supplementation

Maternal vitamin D intake during pregnancy increased the risk for asthma and had no effect for AR in the offspring. Early introduction of fish has repetitively been shown to decrease the risk of AR, and also of asthma, besides other foods (e.g. wheat, rye, oats, barley cereals, egg). A murine birch pollen allergy model suggests that administration of *L. paracasei*, a probiotic bacteria during pregnancy/lactation protects the offspring against airway inflammation via TLR2/4-signalling. Human studies are controversial, lately showing no effect of probiotic mixtures for AR incidence until age 5, solely in the group of offspring delivered via caesarian section.

TABLE 1

Genetic and epigenetic studies in allergic rhinitis

Allergic rhinitis	Chromosome	Gene	Possible allergic mechanism
Genetics (GWAS)	19p13	MRPL4	Involved in inflammatory adhesion process
	10q24	BCAP	Involved in activation, development and maturation of B cells
	11q13	C11orf30/ LRRC32	Epithelial barrier function/regulatory T-cell functions and immune tolerance
	7p21	FERD3L	Unknown
Epigenetics	Selection of relevant CpGs confirmed by pyrosequencing: Function		
	PIEZO1 promoter CpG, RPP21 promoter CpG, HLA-DMA promoter CpG		

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8 THE FARM EFFECT AND ALLERGIC RHINITIS

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KEY MESSAGES

- The association between exposure to a traditional farming environment and protection from allergic disease is extremely robust across studies, countries and continents
- Exposure to cows, straw, and farm milk explains the farm effect for asthma, and exposure to fodder storage rooms and manure explains it for atopic dermatitis. However the farm effect for hay fever and atopic sensitization could not be completely accounted for by these exposure and remains partially unexplained
- The relationship between farm exposure and allergy/hay fever prevalence is extremely dynamic over time, pointing to the impact of rapidly changing environments on allergy risk
- Continued exposure might be a critical component of the protective effects of farming

The association between exposure to a farming environment and protection from allergic disease (among which allergic rhinitis/hay fever is paradigmatic) has proven extremely robust across studies, countries and continents, especially in work focusing on truly traditional farms. A recent, large (>8,000 children) study that sought to identify distinct exposures that account for the protective effect of farming found that children living on a farm were at significantly reduced risk of hay fever (aOR, 0.43; 95% CI, 0.36-0.52; P< .001) and atopic sensitization (aOR, 0.54; 95% CI, 0.48-0.61; P< .001) compared with nonfarm children. Of note, whereas this overall farm effect could be explained by specific exposures to cows, straw, and farm milk for asthma, and exposure to fodder storage rooms and manure for atopic dermatitis, the farm effect on hay fever and atopic sensitization could not be completely explained by the questionnaire items themselves or their diversity. Therefore, the link for hay fever and atopy is still missing. Interestingly, a high number of siblings, especially older siblings, reduces hay fever risk in childhood, and farming families are typically larger in size. However, an inverse association between farm exposure and hay fever was found in all sizes of family, with no substantial tendency to saturation or synergism. This suggests that these two protective factors may act through distinct biological mechanisms.

How strikingly dynamic the relationship between prevalence of allergy and farming can be is eloquently illustrated by the results of two surveys performed in 2003 and 2012 in lower Silesia, Poland (Figure 1). In 2003, among those living in Sobótka (a town of just 4000 inhabitants) the prevalence of atopy was 20%, that is, similar to that observed in the United Kingdom and similar to European countries. In contrast, among those living in any of seven small villages, each no more than 10 km from the town, the prevalence of atopy was just 7%, that is, lower than any recorded elsewhere in Europe. At that time, 55% of villagers (but <1% of those living in Sobótka) described themselves as living on farms. A quarter had regular or occasional contact with cows, a third had regular or occasional contact with pigs, and 35% reported that they drank unpas-

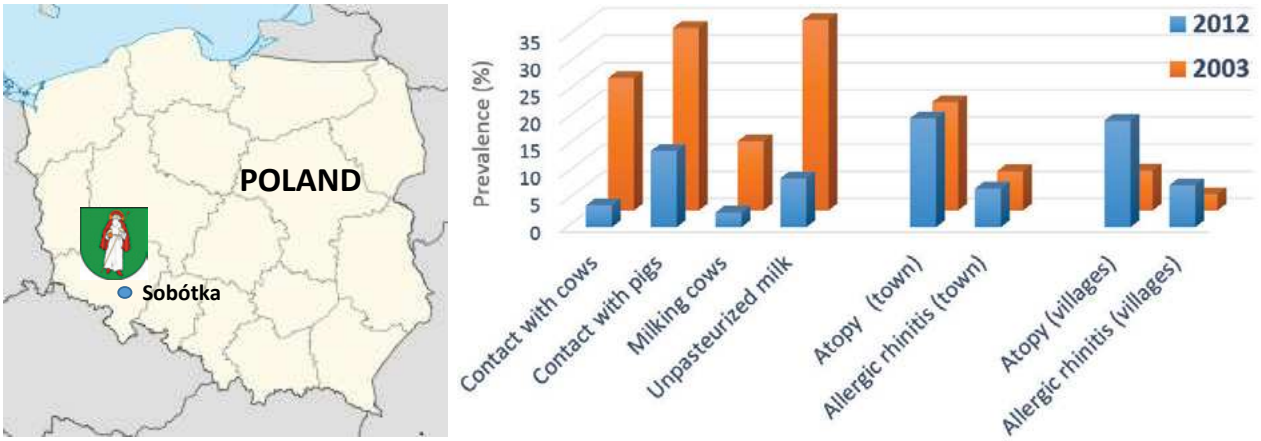

Figure 1 Effects of changing environments on the prevalence of atopy and allergic rhinitis: Results from the 2003 and 2012 Sobotka studies.

teurized cow's milk.. In 2004, Poland joined the European Union and consequently adopted the Common Agricultural Policy. As a result, it immediately became uneconomic for village farmers in Silesia to keep small numbers of cows or other large farm animals. The number of cows and pigs kept by households in the seven villages decreased by 80%. When, in 2012, a second survey of the same area was undertaken, the results were impressive. Far fewer villagers had contact with cows (4% vs 24.3% in 2003) or pigs (14% vs 33.5%), milked cows (2.7% vs 12.7%), or drank unpasteurized milk (9% vs 35%). In parallel, the prevalence of atopy significantly increased among the villagers (7.3% vs 19.6%, P < .0001) but not among the townspeople (20% vs 19.9%). Hay fever increased over 2-fold in the villages (3.0% vs 7.7%) but not in the town (7.1% vs 7.2% (Figure 1). It is especially noteworthy that increased allergy prevalence was detected across all ages.

The dramatic increase in the prevalence of allergies observed in Poland within 9 years, and similar findings from urban Germany after reunification (where the prevalence of atopy doubled within 3 years), suggest that the atopic state is more plastic than many believe in both childhood and adulthood, and highlight the impact of rapidly changing environments on allergy risk. They also suggest that continued exposure might be a critical component of the protective effects of farming.

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9 VITAMIN D AND ALLERGIC DISEASES

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KEY MESSAGES

- Vitamin D is synthesised following sunlight exposure, but small quantities can be ingested
- Vitamin D deficiency is a global problem and has increased markedly in recent decades
- Observational studies highlight an association between vitamin D deficiency and increased incidence of allergic sensitization and disease
- Effects of vitamin D on airways and immune cells are likely to underpin associations between low vitamin D status and allergic sensitization
- Interventional studies are needed to determine whether restoring vitamin D sufficiency improves disease management and reduces the incidence of disease

Environmental factors, such as vitamin D deficiency, are proposed to contribute to the increase in allergic diseases reported in the last half-century. Vitamin D is synthesized following exposure of skin to UVB radiation, and is also present in certain foods and dietary supplements (Figure 1). Vitamin D status is assessed as circulating levels of the major metabolite, 25-hydroxyvitamin D3 (Table 1). Vitamin D deficiency has increased dramatically in recent decades related to changes in lifestyle, including reduced sun exposure.

Vitamin D deficiency, particularly in pregnancy and childhood, is associated with increased allergic sensitization and levels of aeroallergen specific IgE, as well as increased incidence of atopic dermatitis (AD), allergic rhinitis (AR), food allergy (FA) and asthma. However, these data remain contentious since examples of lack, or even inverse correlations, also exist. A non-linear relationship exists between vitamin D status and IgE levels, which may partially explain this discrepancy.. In pregnancy vitamin D assessments are variously made by food-frequency questionnaire, or by single measurements of serum 25-hydroxyvitamin D3 in late pregnancy or in cord blood. The associations are strongest with food-frequency questionnaire, which may represent a more accurate measure of long-term dietary intake.

Vitamin D classically mediates calcium homeostasis and bone metabolism.

The vitamin D receptor is expressed essentially by all immune cells. Furthermore, innate immune cells (e.g. epithelial cells, macrophages, dendritic cells) can convert the precursor 25-hydroxyvitamin D3 to the active metabolite 1α,25-dihydroxyvitamin D3 (Figure 1), supporting a role for extra-renal synthesis of vitamin D and regulation of immune function.

Vitamin D modulates many aspects of immune function (Figure 2). Vitamin D enhances innate antimicrobial mechanisms that aid pathogen clearance, increases the frequency of CD4+IL-10+ and CD4+Foxp3+ regulatory T cell subsets, and inhibits pro-inflammatory Th1 and Th17 responses, both directly and via effects on antigen presenting cells. However, vitamin D can enhance allergy-associated Th2 responses experimentally, even though observational studies demonstrate

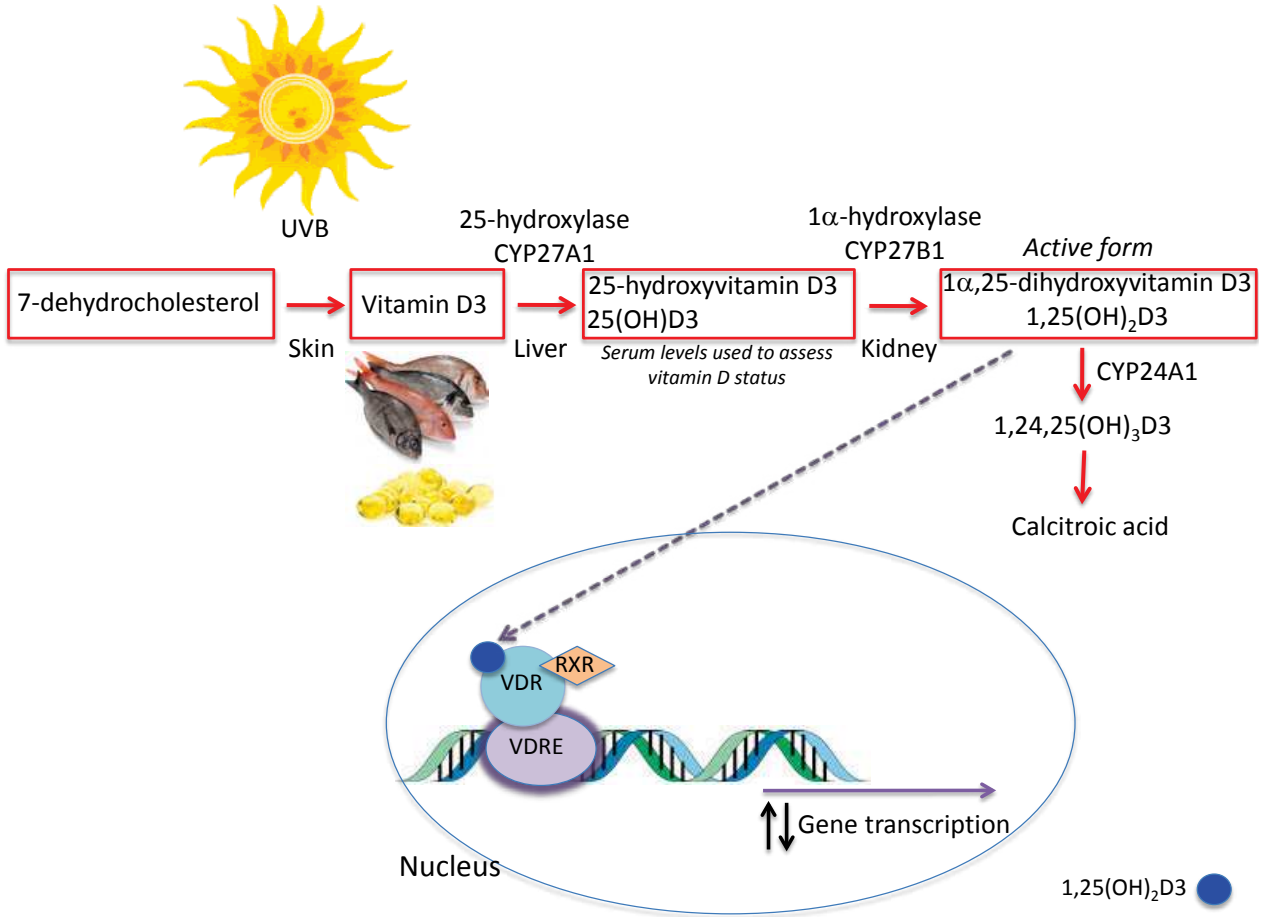

Figure 1 Scheme of the vitamin D metabolic pathway. Vitamin D3 is obtained from dietary sources, or more commonly metabolized following ultraviolet B (UVB) irradiation (from sunshine) of 7-dehydrocholesterol in skin. The enzyme 25-hydroxylase (CYP27A1) in the liver converts vitamin D3 to the major circulating metabolite 25-hydroxyvitamin D3 (25(OH)D3), and then 1α-hydroxylase (CYP27B1), in the kidney and locally in tissues, to the active moiety 1α,25-dihydroxyvitamin D3 (1α,25(OH)$_2$D3). 1α,25-dihydroxyvitamin D3 binds to the vitamin D receptor (VDR), which forms a heterodimer with members of the retinoic acid (RXR) family; this complex translocates to the nucleus and engages the vitamin D response element (VDRE) to mediate gene transcription. 1α,25-dihydroxyvitamin D3 is rapidly inactivated by CYP24A1 to 1,24,25(OH)$_3$D3 and calcitroic acid.

TABLE 1

Vitamin D status			
Vitamin D status	**ng/ml 25-hydroxyvitamin D3**	**nmol/L 25-hydroxyvitamin D3**	**Clinical associations**
Deficiency	Less than 20	Less than 50	Rickets, osteomalacia
Insufficiency	20-30	50-75	Wide range of immune-mediated conditions including allergic sensitization, allergic rhinitis & asthma
Sufficiency	Greater than 30	Greater than 75	

Vitamin D status is measured as circulating levels of the major metabolite, 25-hydroxyvitamin D3. Levels below 50nmnl/L (<20ng/ml) are commonly considered as deficient, 50-75nmol/L (20-30ng/ml) insufficient, and between 75-120nmol/L as sufficient. There is an ongoing debate about the precise levels that constitute sufficiency, however there is consensus that a high prevalence of deficiency and insufficiency exists globally. Vitamin D status is also influenced by skin colour, obesity, season and lifestyle, as well as by genetic diversity.

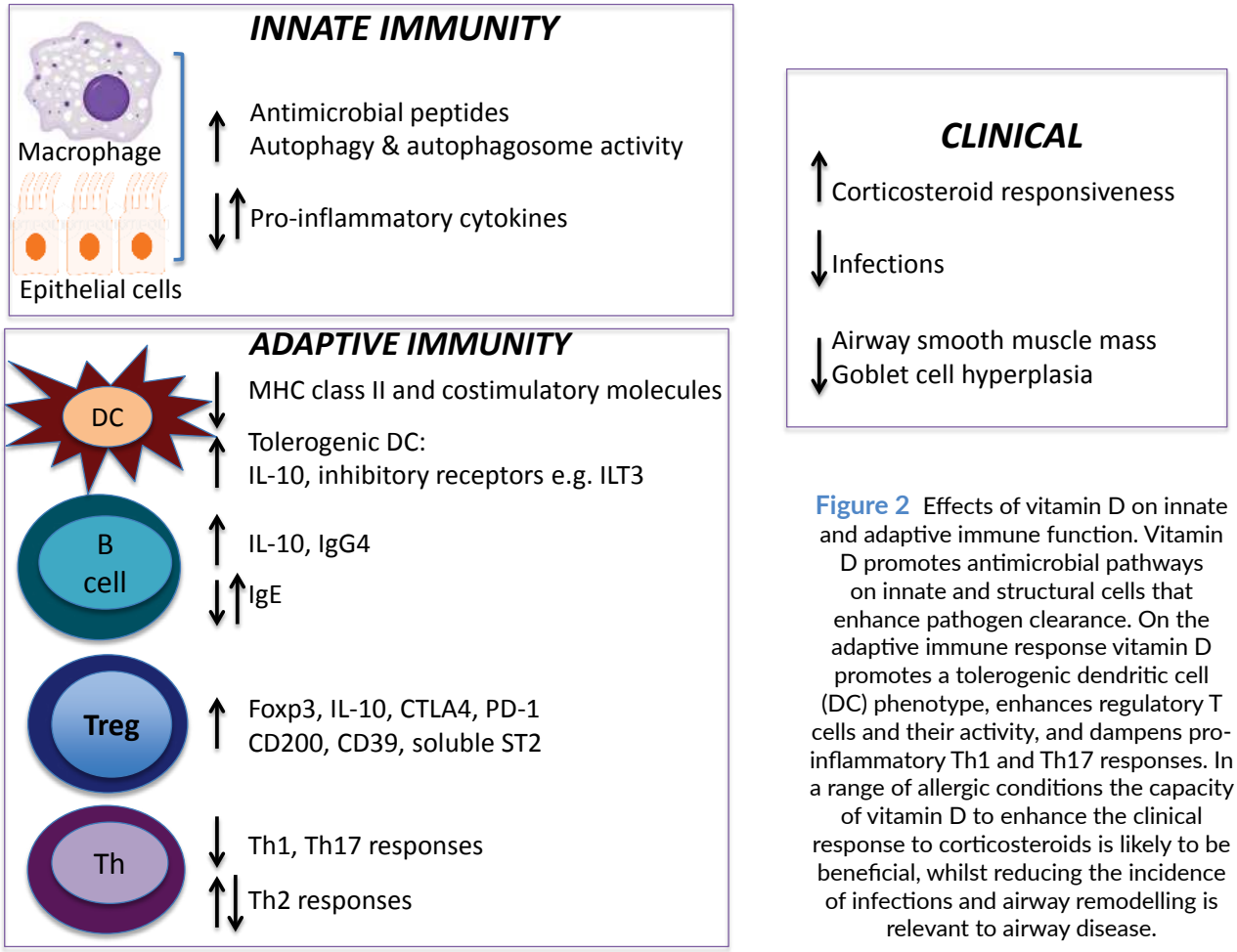

Figure 2 Effects of vitamin D on innate and adaptive immune function. Vitamin D promotes antimicrobial pathways on innate and structural cells that enhance pathogen clearance. On the adaptive immune response vitamin D promotes a tolerogenic dendritic cell (DC) phenotype, enhances regulatory T cells and their activity, and dampens pro-inflammatory Th1 and Th17 responses. In a range of allergic conditions the capacity of vitamin D to enhance the clinical response to corticosteroids is likely to be beneficial, whilst reducing the incidence of infections and airway remodelling is relevant to airway disease.

an inverse association between vitamin D status and Th2-associated allergic diseases. The capacity to enhance regulatory mechanisms, including Th2-specific inhibitory pathways such as soluble ST2, may explain this apparent paradox. Vitamin D also enhances the effects of corticosteroids, which are a primary treatment for many allergic conditions.

Interventional studies are beginning to emerge, and although highly variable in design and outcomes measured, will be essential in evaluating the potential of vitamin D to prevent and control allergic disease.

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10 THE ENVIRONMENT-PATHOGEN-HOST AXIS IN ALLERGIC RHINITIS

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ALLERGIC RHINITIS: THE MOST COMMON MANIFESTATION OF ATOPY

According to WAO estimates, the incidence of allergic rhinitis (AR) ranges from 10-30% worldwide. The tremendous rise in incidence during the last decades emphasizes the importance of environmental factors in the manifestation of the disease. In order to develop prevention measures for people at risk, effort has been put into the identification of genetic and environmental risk factors.

KEY MESSAGES

- Allergic rhinitis (AR) is the most common clinical manifestation of atopy
- Development of AR is controlled by a complex interaction of genetic, environmental and life-style factors
- Environment-environment interactions and climate change related effects are likely to result in higher prevalence of AR
- Early life crosstalk of innate immune receptors with pathogens and the body´s own microbiome contribute to the decision between tolerance and disease

GENETIC PREDISPOSITION

In genome-wide association studies (GWAS), single nucleotide polymorphisms (SNPs) associated with AR were identified. The respective genes – among them IL-18, LRRC32, TLR6, TSLP and NOD1 – govern mechanisms involved in innate immunity, immune regulation and crosstalk of epithelial cells and immune cells (figure 1). Epithelial barrier genes were not identified. This implies that they might play a more prominent role in atopic eczema and in asthma than in AR. In contrast to other atopic traits, the genetic susceptibility to AR seems less clear. This is likely due to fact that patients with AR often develop asthma, resulting in an overlap of phenotypes. In line with this, some results were not replicated in meta-analyses.

ANTHROPOGENIC ENVIRONMENTAL FACTORS

Anthropogenic environmental factors, such as air pollutants, can impact directly on human health, but can also indirectly influence patients via their interaction with allergens (environment-environment interactions) (figure 2). For the direct effects, population-based studies show relationships between allergic sensitization/AR symptoms and long-term exposure to traffic-related air pollutants, such as Diesel exhaust particles, fine particulate matter, NO_2 and ozone. However, a recent meta-analysis did not show any clear correlation between AR and anthropogenic pollutants. These inconsistencies likely reflect methodological differences. in study design, measurement of pollutant exposure or differences in outcome between short-term and long-term exposure. For the indirect effects on human health, ozone was shown to enhance the allergenicity of birch pollen, a highly relevant allergen for AR. Moreover, prolonged flowering seasons and increases in pollen load as a consequence of global warming might increase AR burden.

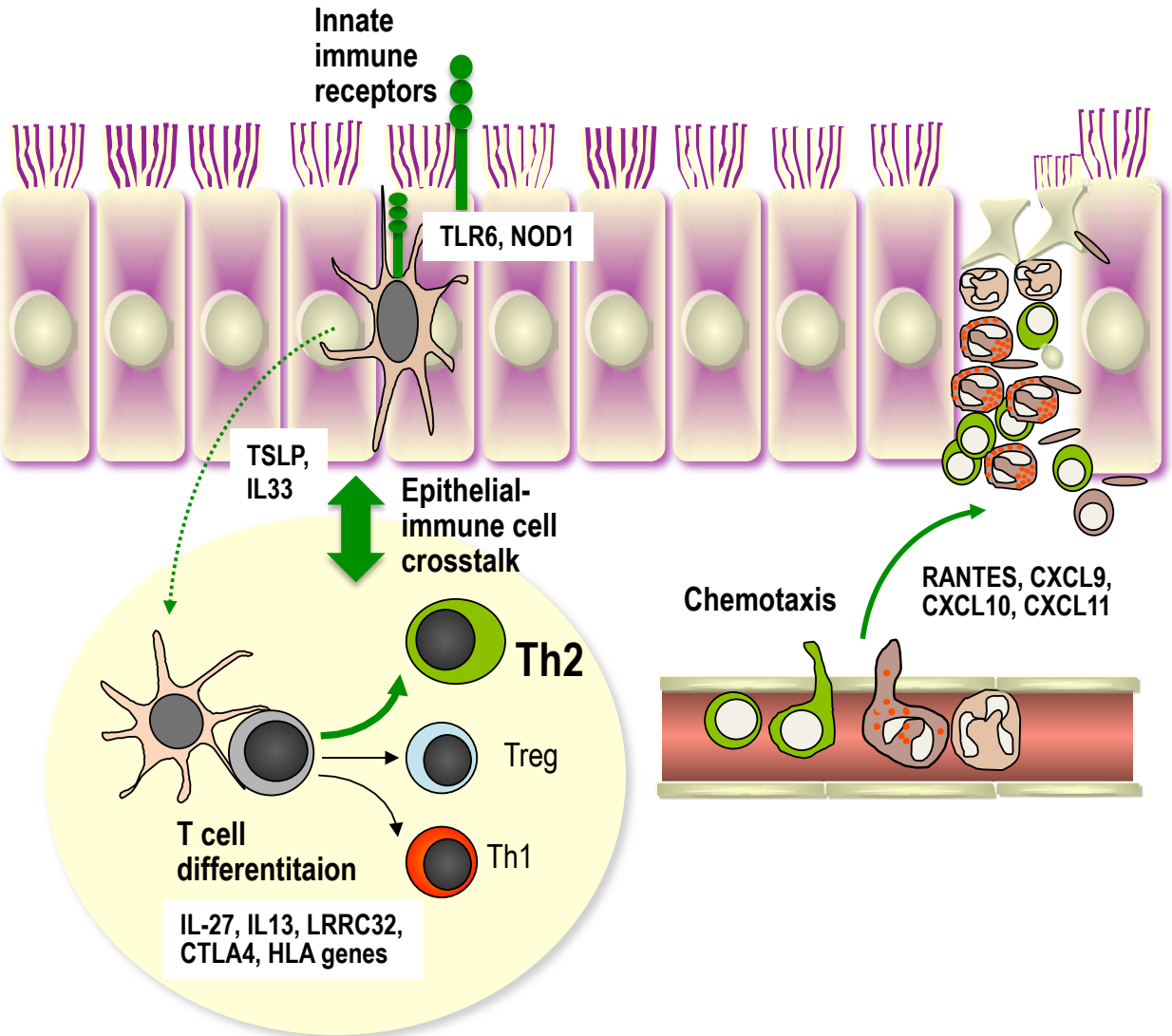

Figure 1 Genes associated with the allergic rhinitis phenotype. Genome-wide association studies identified polymorphisms in several genes that may be linked to allergic rhinitis (AR). These genes are involved in different steps of the pathomechanism of AR, i.e. recognition of pathogen-associated molecular patterns, epithelial cell-immune cell crosstalk, T helper cell differentiation and immune cell chemotaxis. Legend for figure 1: CTLA4 = cytotoxic T-lymphocyte-associated protein 4; CXCL= the CXC-chemokine ligand; IL = interleukin; LLRC = Leucine-Rich Repeat-Containing Protein 2; NOD = nucleotide oligomerization domain; RANTES = Regulated on Activation, Normal T Cell Expressed and Secreted; Th = T-helper cell; TLR = Toll-like receptor; Treg = T regulatory cell; TSLP = Thymic stromal lymphopoietin.

BIOGENIC ENVIRONMENTAL FACTORS

The world-wide rise in allergic diseases parallels the "western-ized" life-style, characterized by increasing urbanization, smaller family sizes with fewer siblings, improved hygiene standards, increasing numbers of cesarean sections, changed dietary habits and excessive use of antibiotics. This association gave birth to the "hygiene hypothesis", which states that early life exposure to certain environmental microbes or pathogens confers protection against allergic diseases later in life. However, to be protective, an environmental factor has to encounter a susceptible genotype (figure 3). This is exemplified by a study

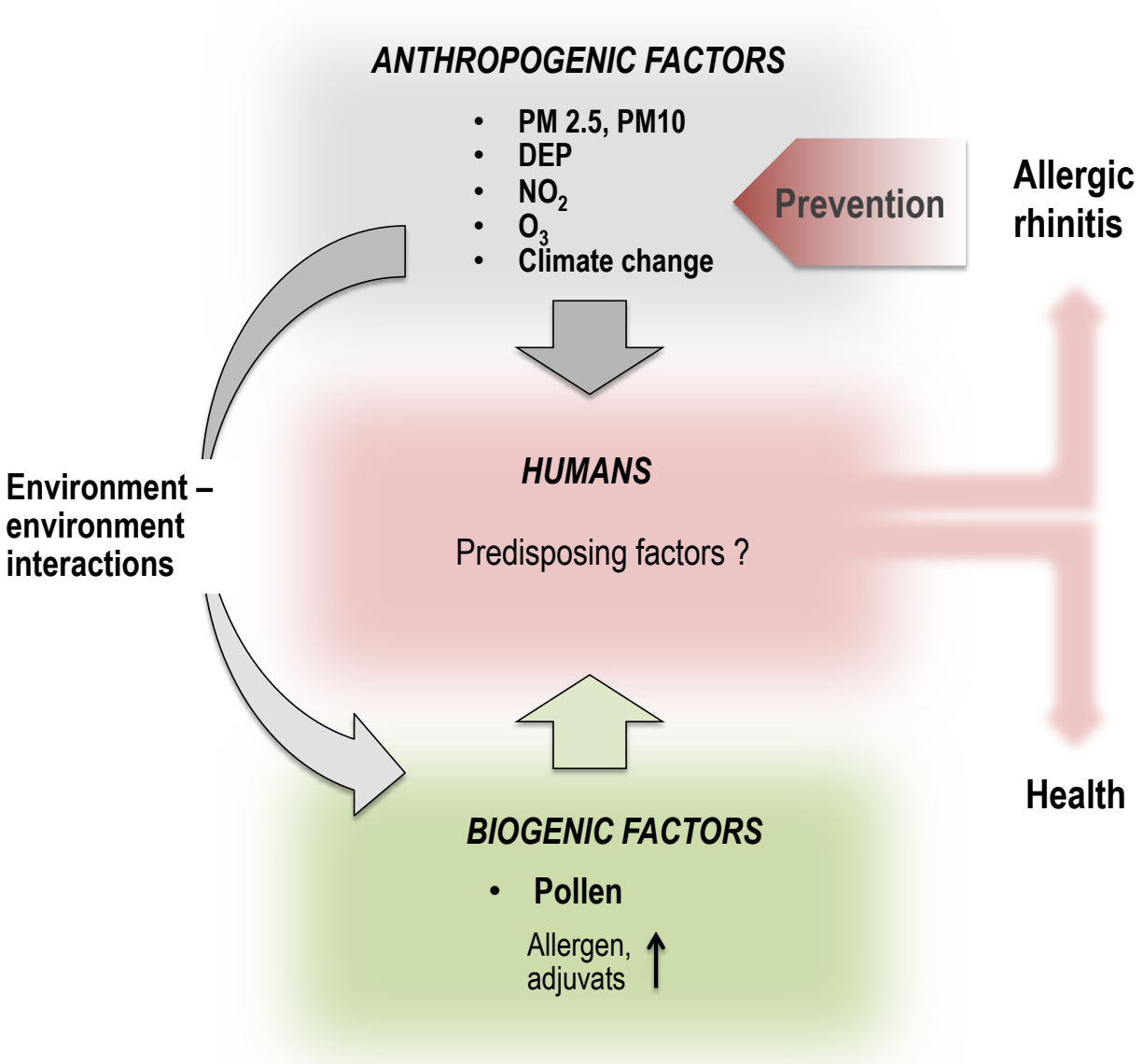

Figure 2 Effect of anthropogenic air pollution and climate change on allergic rhinitis. Traffic-related air pollutants associated with the development of AR include particulate matter (PM), Diesel exhaust particles (DEP), nitrogen dioxide (NO_2), and ozone (O_3). These pollutants have a direct effect on asthma and cardiovascular diseases. Their effect on AR remains ambiguous. However, air pollutants enhance the expression of allergenic proteins and adjuvants in pollen, and can therefore influence AR patients indirectly. Global warming might contribute to the rising trend in allergies due to increases in allergenic pollen load. Legend figure 2: DEP = Diesel exhaust particle; PM = particulate matter.

demonstrating that the protective effect of early life farm milk consumption on allergic diseases was stronger in children carrying a certain allele for the innate immune receptor CD14.

CONCLUSIONS

Like other diseases linked to atopy, AR is caused by genetic as well as environmental and life style factors. By revisiting the "hygiene hypothesis", it becomes increasingly clear that the developing immune system is shaped by pre-natal or early life exposure to pathogens and colonizing microbiota. In genetically predisposed individuals, disturbance of this intricate crosstalk causes immune dysregulation, resulting in autoimmunity or allergy.

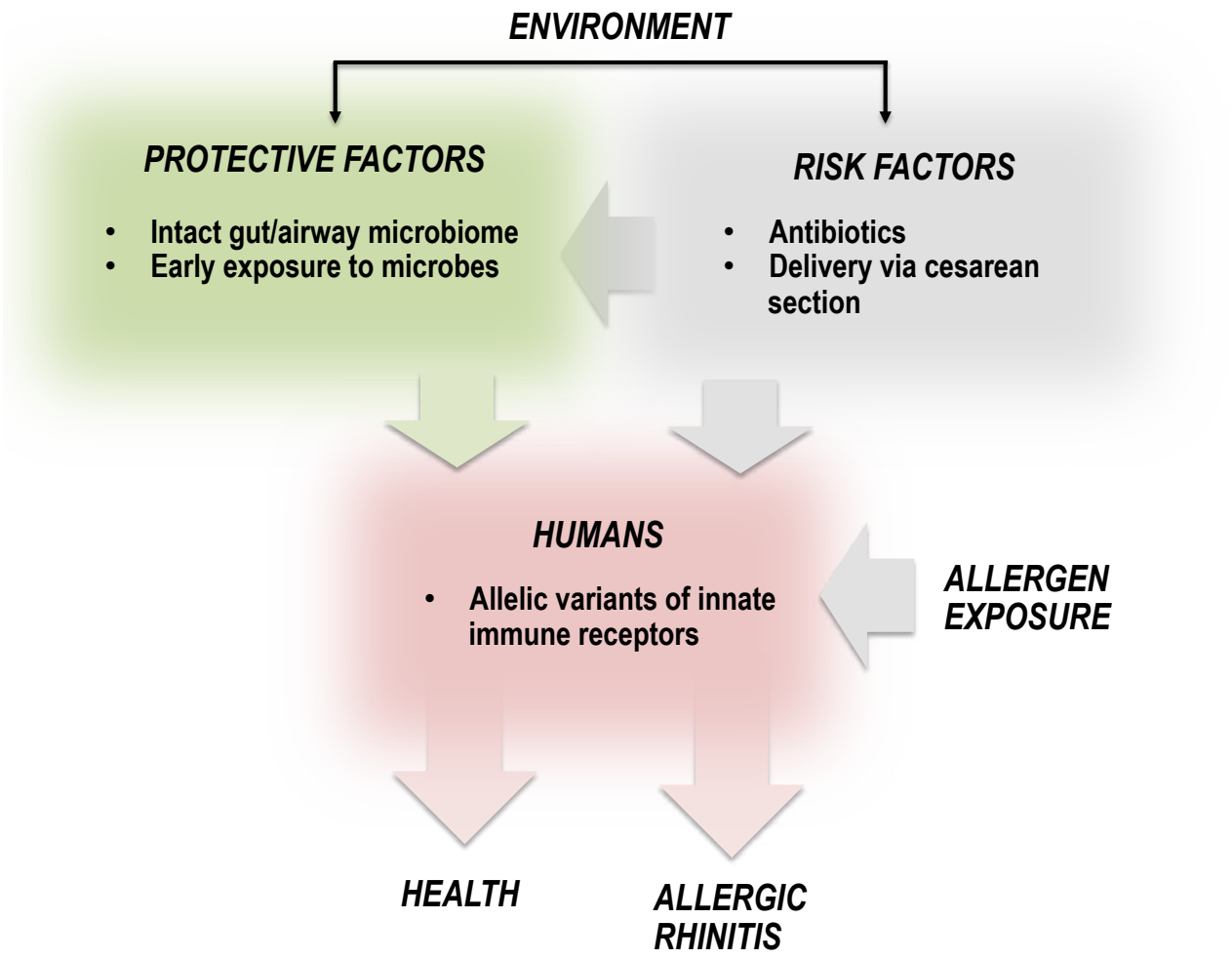

Figure 3 Harmful and protective environmental factors for the development of allergic rhinitis. AR is a complex disease triggered by genetic and environmental factors. Protection is conferred early in life when a favorable genetic background encounters protective environmental factors, such as an intact microbial flora and certain microbial pathogens. In contrast, allergen exposure induces allergic disease if an unfavorable genetic background meets harmful environmental factors, such as an imbalanced microbial flora. Cesarean section delivery and excessive antibiotic use can alter the body´s microflora and might therefore cause immune dysregulation.

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11 THE NASAL MICROBIOME

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KEY MESSAGES

- Microbes start to colonize all of our body surfaces after birth
- The microbiota changes with age and is shaped by environmental exposures, lifestyle and inflammation
- Many bacterial 'pathogens' are normal components of the microbiota, which under certain circumstances outgrow and can cause disease
- New approaches that target interactions between the microbiota and host inflammatory pathways could help reduce the global burden of allergic diseases

THE "HUMAN SUPERORGANISM"

Microbes reside in niches throughout our body (Figure 1), and host-microbe interactions play a fundamental role in immune and disease development. Indeed, the 'human superorganism', consists of 1% human DNA and 99% microbial DNA. The nasopharyngeal microbiota has been well described, is considered distinct from other body sites, and amongst its constituents are bacteria that are considered pathogens, for example, *Streptococcus pneumonia*, *Haemophilius influenza*, *Staphylococcus aureus* and *Moraxella catarrahlis*. However, overt disease is typically not evident unless these bacterial species become dominant at the expense of other resident microbes. This is a state of 'dysbiosis' and is often associated with inflammation. The factors that allow this microbial dysbiosis to develop could be key to a deeper understanding of disease aetiology, susceptibility and future therapeutic or prevention strategies.

FACTORS SHAPING THE CONSTITUENTS OF THE MICROBIOTA

Many factors can modulate the composition of the nasopharyngeal microbiota, such as vaccination strategies and exposure to microbes present in different environments/ climates/ seasons. As examples, studies have shown that respiratory tract viral infections can profoundly impact on local bacterial populations, and that the microbiota is different between summer and winter. Recently, the development of the upper respiratory tract microbiota was tracked over the first 2 years of life, and found to develop and cluster into certain groups. For example, breast-feeding was associated with a more stable microbiota with high abundance of *Moraxella* and *Corynebacterium/ Dolosigranulum*, and lower incidences of parental-reported respiratory infections. Comparatively, less stable microbial profiles were linked with high abundance of *Haemophilus* or *Streptococcus*. Studies of the nasal microbiota of individuals with or without allergic rhinitis have clearly showed that this disease is associated with changes in microbial diversity and constituents. Is this cause or effect? Do certain microbes predispose to allergies, or do allergies create tissue environments suitable for these microbes?

OUTLOOK

Further studies are required to distinguish cause-and-effect from simple associations, however an emerging theme is that bacteria, classically considered pathogens, are normal residents of the res-

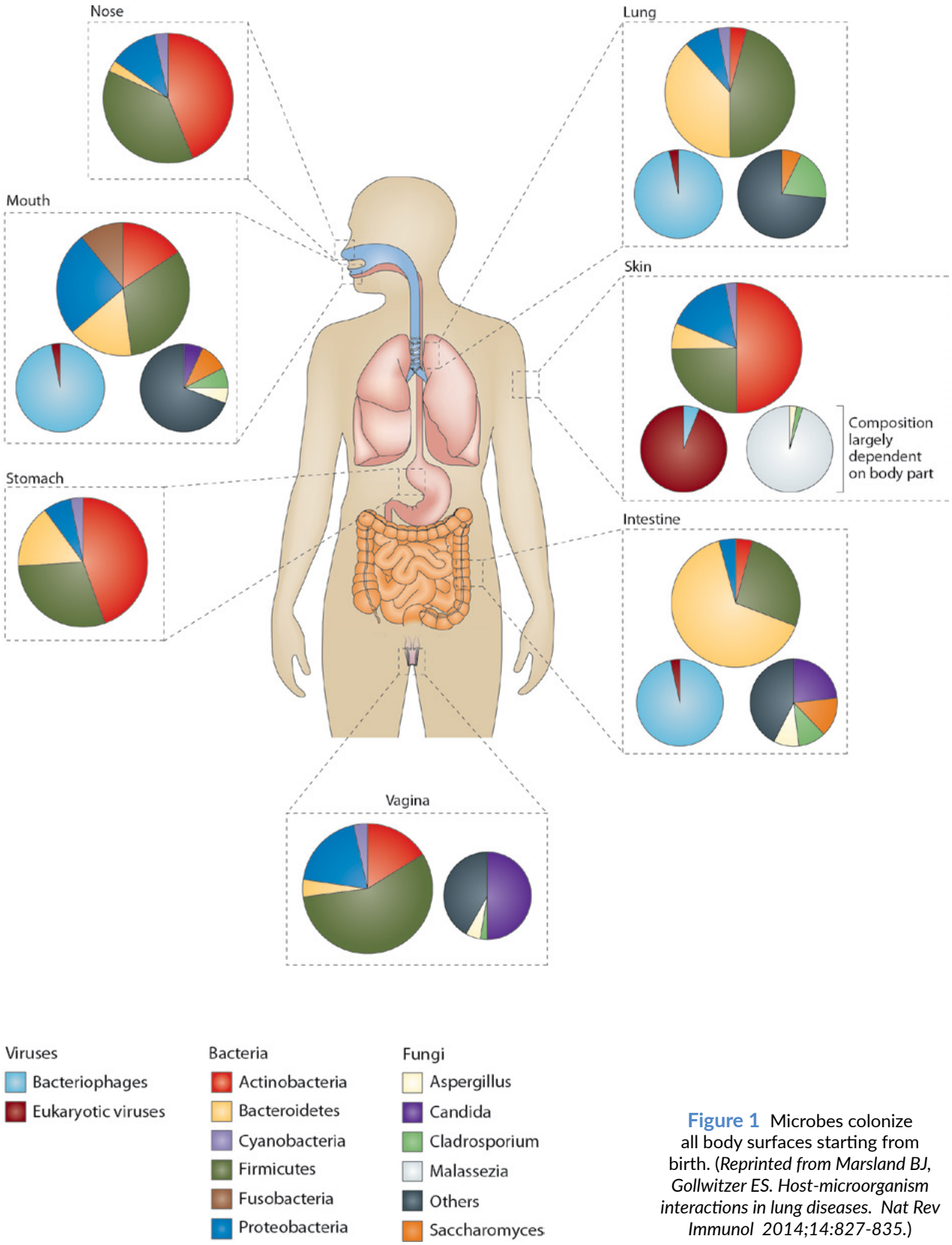

Figure 1 Microbes colonize all body surfaces starting from birth. (*Reprinted from Marsland BJ, Gollwitzer ES. Host-microorganism interactions in lung diseases. Nat Rev Immunol 2014;14:827-835.*)

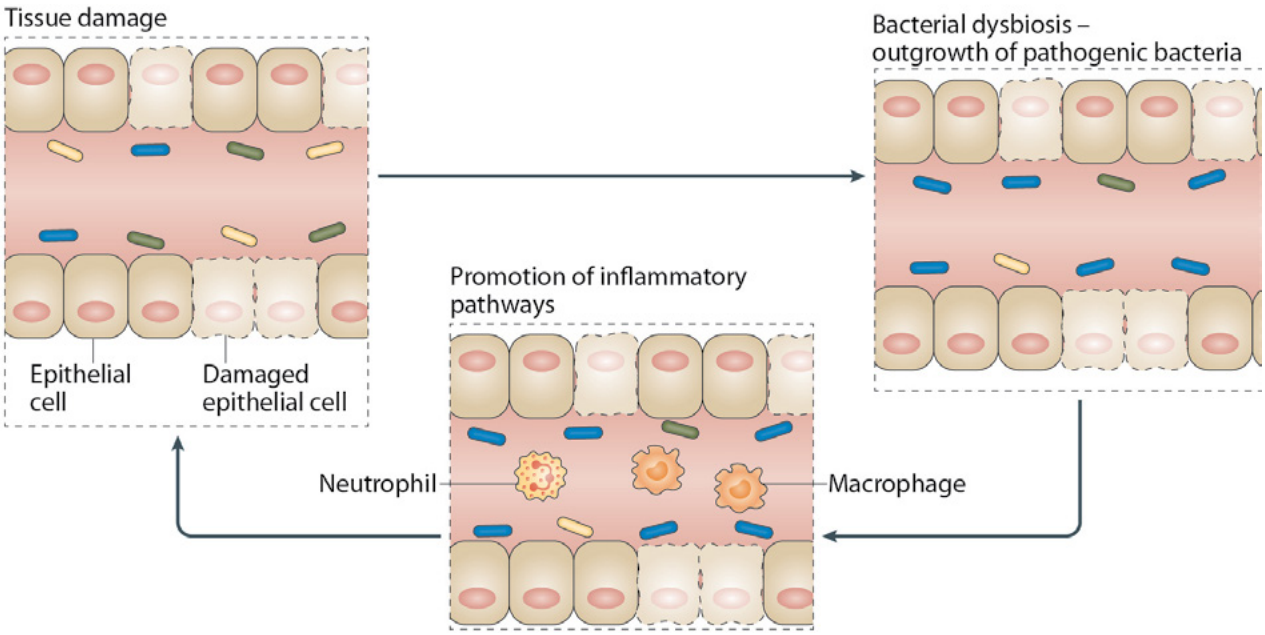

Figure 1 Cross-talk between inflammatory pathways and microbes can create a tissue environment suitable for outgrowth of resident pathogens that further increase inflammation and disease pathology. (*Adapted from Marsland BJ, Gollwitzer ES. Host-microorganism interactions in lung diseases. Nat Rev Immunol 2014;14:827-835.*)

piratory tract and that certain events may change this habitat allowing for them to expand and promote disease. There is clear crosstalk between microbes and inflammatory pathways (Figure 2); a greater appreciation and understanding of the interactions between the tissue environment, microbes and inflammation may lead us to approaches that will reduce the global burden of allergies.

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12 UPPER RESPIRATORY TRACT INFECTIONS IN CHILDHOOD ARE LINKED TO THE DEVELOPMENT OF ALLERGIC RHINITIS IN ATOPIC CHILDREN

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KEY MESSAGES

- Upper respiratory tract infections in early childhood may be protective against the development of allergic rhinitis (AR) in the general population
- However, upper respiratory tract infections are associated with the development of AR in children with atopic family histories
- Children with an atopic phenotype have decreased virus-induced interferon-alpha production. This reduction in innate immune anti-viral responses may predispose them to develop AR that results from frequent URTIs

Many clinicians and parents question whether frequent upper respiratory tract infections (URTIs) in early childhood can increase the risk for the development of allergic rhinitis (AR). Frequent URTIs are defined as viral infections of the nose or ears occurring more then six times per year. AR is a combination of congestion, sneezing, and rhinorrhea with associated pruritus of the nose and eyes due to demonstrable aeroallergen sensitivity.

The link between infection and the development of AR is complex, exemplified by the inconsistent and conflicting results of various epidemiologic studies. These observed discrepancies appear to be due to variability of host factors. Some studies show an inverse association between URTIs and AR, while others show no association. Interestingly, any observed association or increased risk appears to be greater in children with a family history of atopic disease. Indeed, these children show increased rates of atopy if they experience early URTIs.

In observations supporting the hygiene hypothesis, Svanes et al found the number of siblings at home and day care enrollment was inversely proportional to the risk of AR development. Assuming that the number of siblings and day care could be surrogate markers for URTI frequency, this study suggested that frequent URTIs in childhood are inversely related to the development of AR.

However, a more recent prospective birth cohort study by Balemans et al found no association between recurrent URTIs in childhood and the development of AR. The authors concluded that URTI in childhood do not reduce the risk of AR in young adulthood. Conversely, Lee et al found that high-risk children with a family history of asthma or atopic sensitization have increased rates of AR when exposed to parainfluenza virus and picornavirus in the first year of life.

The discrepancy in research findings among the various studies may be due to differences in immunologic response profiles in the children experiencing these viral illnesses. For example, children with an atopic phenotype have been shown to have decreased virus-induced interferon (IFN)-alpha production compared to healthy controls. Since IFN-alpha is both antiviral and immunoregulatory, any observed differences could be attributed to differences in these host response patterns. Thus, if a child has an atopic phenotype, their innate immunoinflammatory responses may predispose them to the development of AR.

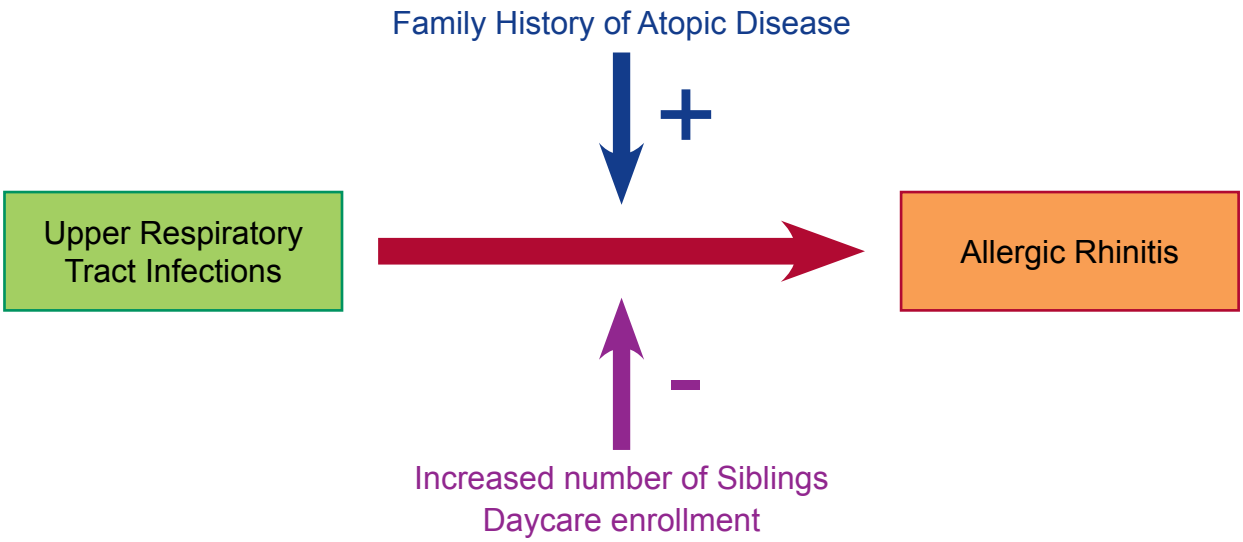

Figure 1 the complex interplay between the host and viral infections is modulated by host factors such as atopic status and by several environmental factors.

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13 THE COMMON COLD IN ALLERGIC INDIVIDUALS

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The **common cold** is a pre-eminent phenotype of infectious rhinitis with high incidence and prevalence, associated with considerable burden and socioeconomic costs. Numerous viruses manifest with common cold symptoms, the most prominent of which is human rhinovirus (HRV), a heterogeneous virus segregated in three groups (HRV-A, B and C) and with over 100 serotypes (Figure 1).

Allergic rhinitis (AR) is often contrasted to infectious rhinitis/common cold, as a rhinitis entity whose pathophysiological mechanism is driven by atopy instead of infection. Although the underlying pathophysiology of common cold and AR is viewed as radically different, their clinical manifestations do not differ much and it is often challenging to set apart these two conditions by clinical criteria. In addition, it appears that allergen-driven and virus-driven inflammation considerably overlap (Figure 2).

HRV infections often interact with AR, or -more appropriately- with the **atopic state** that underpins AR. Indeed, viral infections can trigger bronchial – and apparently nasal – hyperresponsivenes

KEY MESSAGES

- Numerous viruses manifest with common cold symptoms, the most prominent of which is human rhinovirus (HRV)
- Allergic rhinitis (AR) and the common cold in allergic individuals have in common their symptoms and their pathophysiologies are interconnected
- HRV infection is often more severe in atopic individuals, as infection-induced, interferon-mediated innate responses are differentially regulated and viral replication is increased in a Th_2 environment
- Conversely allergen exposure concurrent to infection can lead to an exaggerated allergic reaction

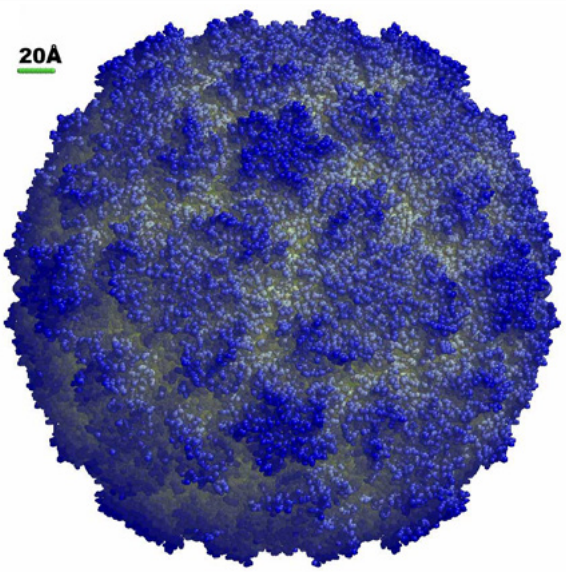

Figure 1 Human rhinovirus type 16. (*Accesed from http://www.virology.wisc.edu/virusworld/ICTV8/r16-human-rhinovirus-16-ictv8.jpg on May 11, 2015.*)

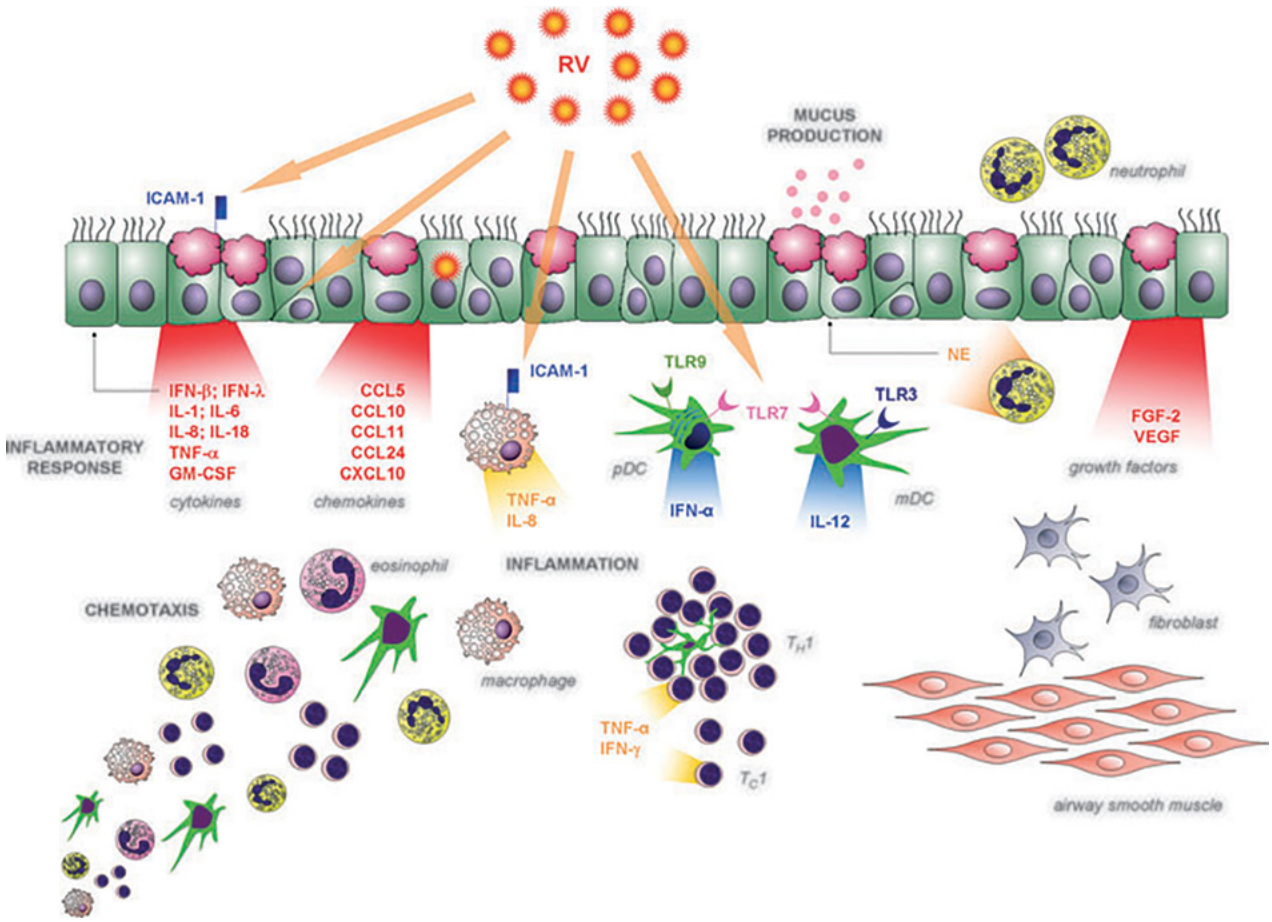

Figure 2 Mucosal response following Rhinovirus (RV) infection. (*Reproduced from Papadopoulos NG, Xepapadaki P, Mallia P, et al. Mechanisms of virus-induced asthma exacerbations: state-of-the-art. A GA2LEN and InterAirways document. Allergy 2007;62:457-470, with permission from Wiley-Blackwell.*)

and increased recruitment and activation of eosinophils in atopic subjects. HRV in particular, causes both bronchial and nasal eosinophilia, which – importantly – is prolonged in asthmatic and rhinitic patients (Figure 3). HRV infection is often more severe in atopic individuals, as infection-induced, interferon-mediated innate responses are differentially regulated in these patients and viral replication is increased in a Th_2 environment. Also, the degree of antibody-mediated protection from HRV infection may be suboptimal in atopic subjects. In fact, it appears that the interactions between HRV and the atopic state could be so robust that the actual presence of allergen is not required for the increased severity of the symptoms of infection. Nevertheless, if a sensitized individual is exposed to the allergen in the context of an HRV infection, an augmented reaction could ensue. Indeed, in AR patients, allergen challenge after an HRV infection leads to increased bronchial eosinophil accumulation and enhanced and persistent release of histamine.

In all, atopy appears to be a risk factor for increased severity of the common cold infection. Inversely, allergen exposure concurrent to infection can lead to an exaggerated allergic reaction. These are important interactions between two pathophysiological mechanisms that, at first look, appear to be different.

AR and the common cold in allergic individuals have more in common than initially meets the eye: their symptoms tend to overlap (as is especially true for rhinorrhoea and sneezing and less so for obstruction and itching) and their pathophysiologies, albeit didactically distinct, are interconnected.

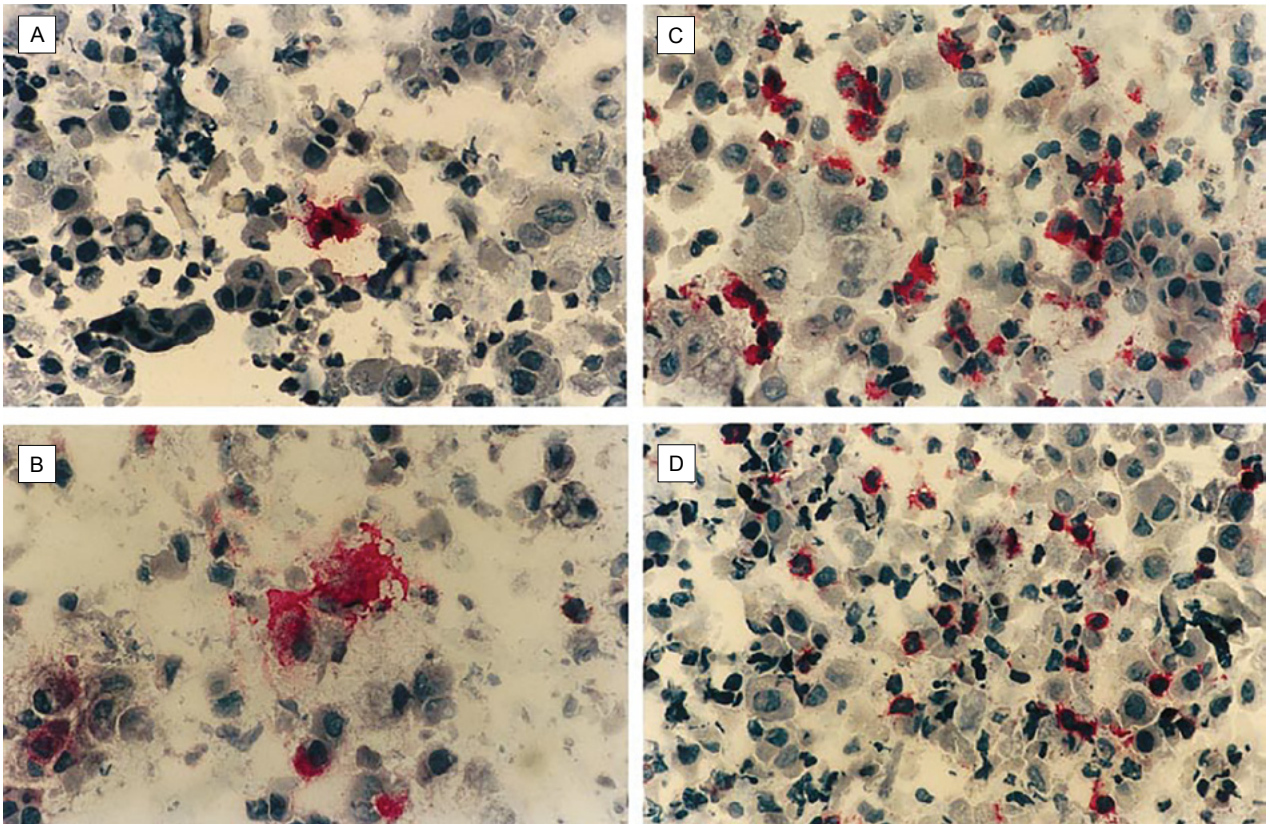

Figure 3 Nasal brush samples following common cold infection, stained for A. MBP (eosinophils). B. Eotaxin C. CD68 (Macrophages) D. CD3 (T cells). (*Reproduced from van Benten IJ, KleinJan A, Neijens HJ, et al. Prolonged nasal eosinophilia in allergic patients after common cold. Allergy 2001;56:949-956, with permission from Wiley-Blackwell.*)

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14 FURRY ANIMALS – RISK OR PROTECTIVE FACTOR FOR ALLERGIC RHINITIS?

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KEY MESSAGES

- Tolerance to animal dander can be seen either as lack of IgE production or as progressive decrease in symptoms with prolonged exposure
- Community prevalence of animal ownership is an important determinant of the levels of cat allergen in schools and homes without a cat
- The impact of a dog in the house is complex because they introduce a wide range of bacteria into the house as well as being a source of allergen

The significance of skin tests or IgE antibodies for cat or dog allergens has been appreciated by physicians who were interested in allergic disease for many years. However, the relationship between exposure to animal allergens and sensitization has been less clear. For many years, it was assumed that cat or dog ownership was the primary factor in specific sensitization. Many allergists in practice went further and say that a positive skin test for cat was only relevant to asthma or allergic rhinitis (AR) if the patient had an animal at home. It was therefore a surprise when Hesselmar et al. reported that subjects living in a house with a cat were less likely to become sensitized to cat allergens. Subsequent studies rapidly confirmed this finding for cats and dogs (Figure 1). At the same time, it became clear that animal dander allergens not only remained airborne in the home but were present in homes without a cat as well as in schools, offices and other public places.

One of the problems with assessing the role of cat allergens in AR is that exposure is perennial and that there are very few studies that have successfully decreased exposure sufficiently to answer questions about the role of cat allergens induced-symptoms. In addition, controlled trials of cat allergen immunotherapy (AIT) for AR have generally not been carried out on allergic subjects who do not have an animal in their house. Investigation of the effects of animal ownership has given different results in different communities. In some studies, the protective effect of cat ownership appeared to be at least partly explained by the removal of pets by families with allergic children. However many studies have confirmed a strong protective effect of early dog or cat ownership.

Since it is clear than many patients who do not live in a house with a cat become sensitized it is important to consider what influences the quantity of cat allergens in schools or homes without a cat. The best data comes from schools in Stockholm, where it has been clearly shown that the quantity of cat allergen in a room is directly related to the number of children in the class who have a cat at home. The obvious implication is that the quantity of cat allergen in homes without a cat is likely to be influenced by the number of the homes in the community where animals are kept. Indeed, in some areas of the United States animals are not kept at all or are kept outside only. In these predominantly, African-American communities, the prevalence of cat allergy is generally very low. Equally keeping any animal that is rare in the community i.e. <2% is not likely to sensitize a significant number of

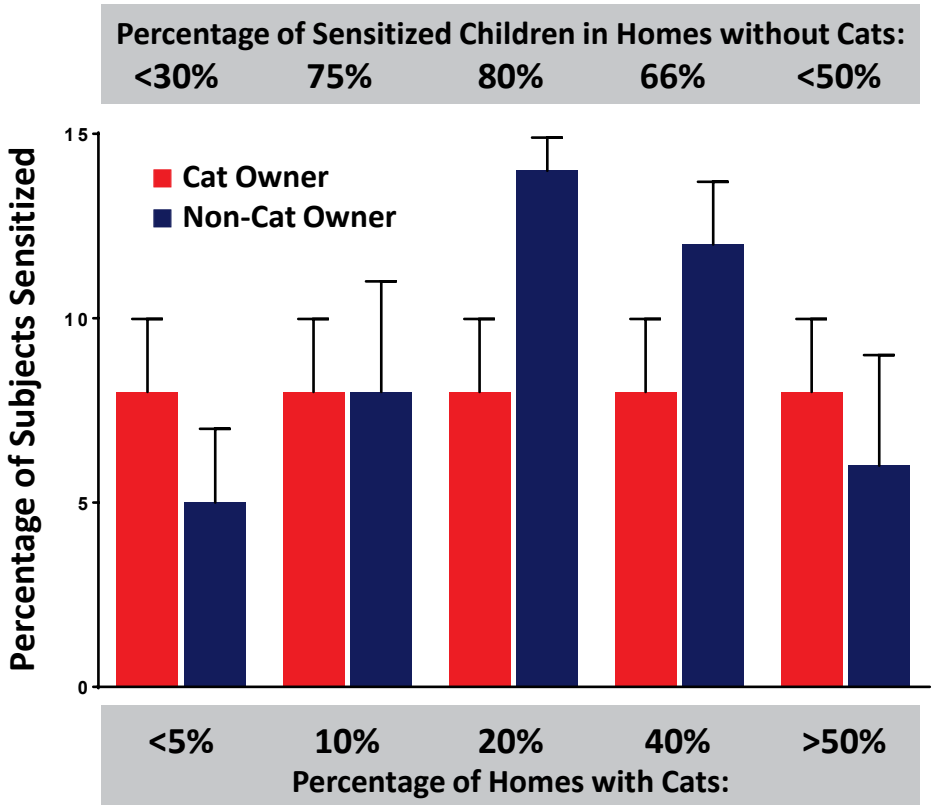

Figure 1 Sensitization to Cat Allergens in Relation to the Prevalence of Cat Ownership in the Community

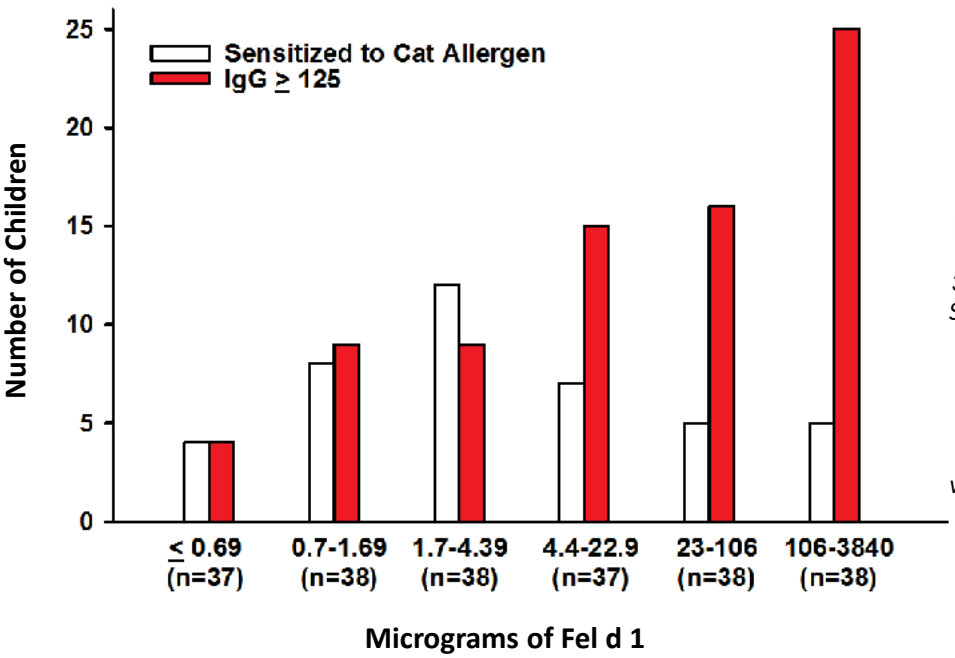

Figure 2 Prevalence of Sensitization and IgG Antibodies to Fel d 1 in 11-year-old Children in Relation to Home Exposure. (*Reprinted from The Lancet, 357, Platts-Mills T, Vaughan J, Squillace S, et al, Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study, 752-756, Copyright 2001, with permission from Elsevier.*)

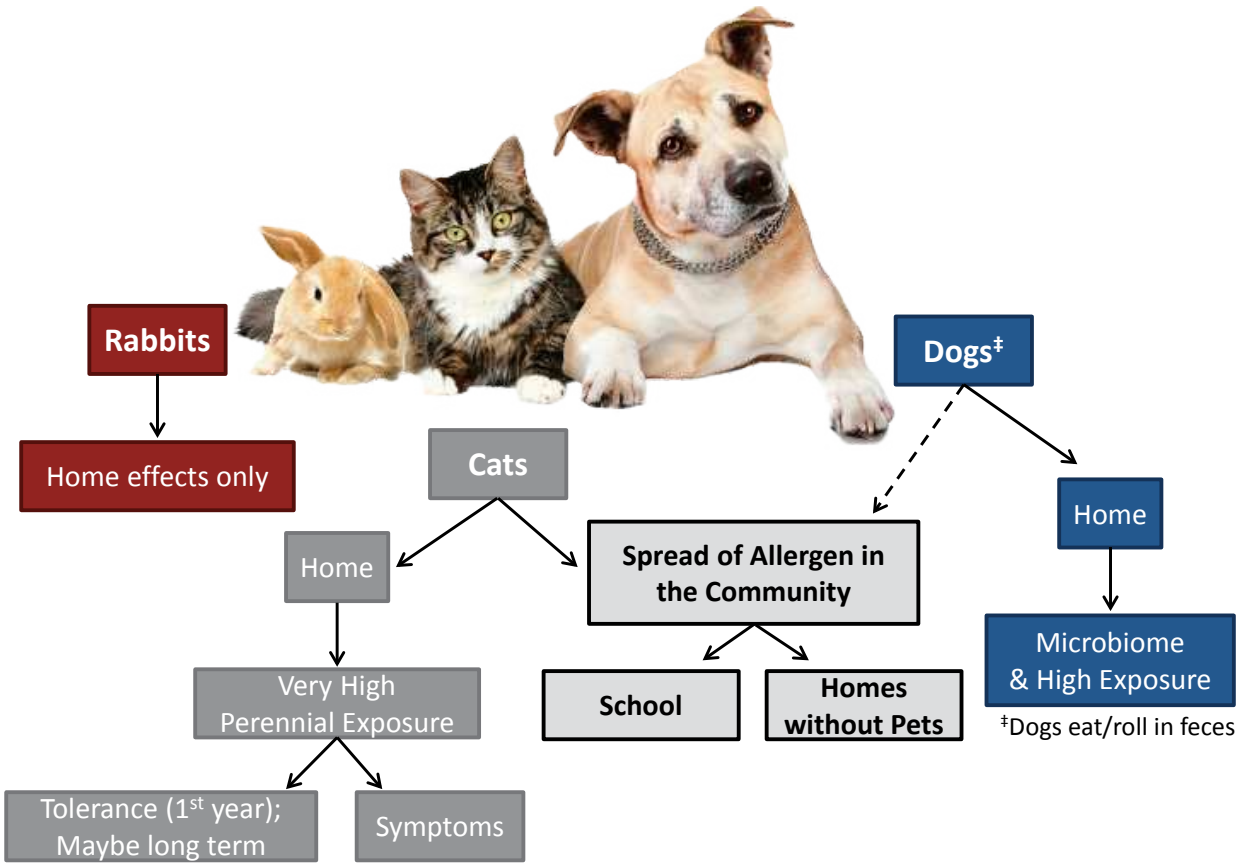

Figure 3 Immune Effects of Furry Animals in the Home and the Community.

children outside the home where the animals is kept.

CONCLUSIONS

All animals produce allergens and can induce specific sensitization. However, a large range of studies shows that in a community where 20% to 40% of the families have a cat, those children without a cat at home are equally if not more likely to be sensitized. Even if the prevalence of sensitization is equal among children without a cat, 80% to 60% of the allergic children will not have an animal at home. Thus the presence of animals in a community can be the or a major risk factor for sensitization even though children who are exposed from early childhood are less likely to become sensitized. By contrast for animals such as rabbits which are much less common in homes, it is the patients who live with the animals that have the main risk. It is clear that the current situation is not simple and not surprisingly it is not easy to make a simple case about the clinical relevance of a positive skin test to animal dander.

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15 ALLERGIC RHINITIS PREVALENCE AND CLIMATE CHANGE: A GLOBAL ECOLOGIC ANALYSIS

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KEY MESSAGES

- Climate change is measurably altering the timing, distribution, quality and quantity of allergenic plants and aeroallergens
- These changes may affect the global distribution of allergic rhinitis (AR) incidence and prevalence as well as symptom severity, but additional research is needed
- Several spatial associations between climatic factors and the prevalence of both intermittent and persistent rhinitis symptoms in children were identified in a recent global ecological study, providing suggestive evidence that climate influences the prevalence of rhinitis symptoms
- Further large multi-country studies that consider climatic effects on different AR phenotypes, and the potential interacting role of air pollutants, are needed

A major potential indirect effect of climate change on public health is predicted to arise via climate-induced changes in aeroallergens, the primary risk factor for allergic rhinitis (AR). There is already a significant body of evidence indicating that climate change is measurably altering the timing, distribution, quality, and quantity of allergenic plants and aeroallergens. Such changes are occurring via meteorological factors and through interactions with greenhouse gases and air pollutants, and may affect both the incidence and prevalence of AR, as well as the severity of symptoms.

Despite the strong evidence demonstrating climate-induced changes on allergenic plants and aeroallergens and the known causal relationship between aeroallergens and AR onset and prevalence, studies examining associations between climatic factors and AR have yielded mostly inconsistent results. This may be because climatic effects on aeroallergens and thus presumably on AR are likely to vary by geography and vegetation type. Studies that incorporate data from several geographical areas and climates are required. However, to date, only very few studies have examined associations between climatic factors and AR using data from more than one country.

The most recent effort utilized data collected by the worldwide International Study of Asthma and Allergies in Childhood survey (3). In addition to identifying variation in the global distribution of both intermittent (Figure 1) and persistent rhinitis symptom prevalences among children, this ecological study reported on several spatial associations between climatic factors and the prevalence of these allergic conditions on a global scale. Associations appeared most consistent for intermittent rhinitis symptoms when examining country-level (between-country, Figure 2) associations, whereas associations with persistent rhinitis symptoms were more consistent at the center-level (within-country associations, Figure 3). The overall trend reported in this paper was a generally positive association between mean monthly temperature and vapor pressure (which were highly correlated) and several measures of precipitation, with rhinitis symptom prevalence.

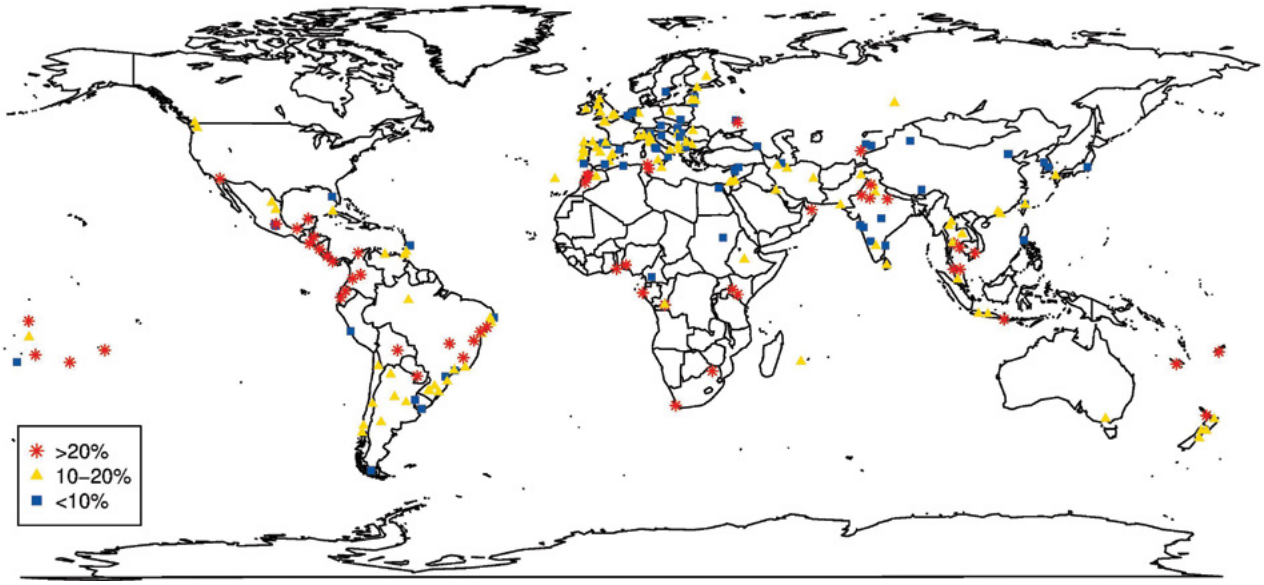

Figure 1 World map showing the center prevalence of intermittent rhinitis symptoms for the centers with 13- to 14-year-olds. (*Reprinted from Ann Allergy Asthma Immunol, 113/4, Fuertes E, Butland BK, Anderson HR, Carlsten C, Strachan DP, Brauer M, Childhood intermittent and persistent rhinitis prevalence and climate and vegetation: a global ecologic analysis, 386-392, Copyright 2014, with permission from Elsevier.*)

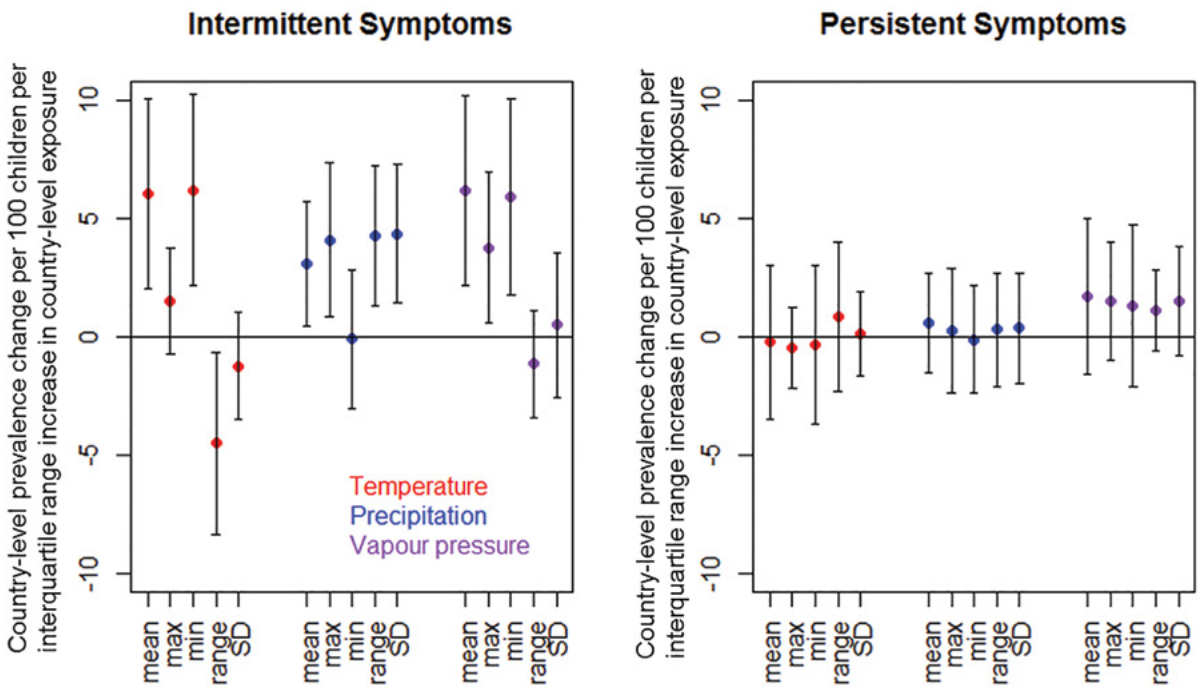

Figure 2 Between-country associations for intermittent and persistent rhinitis prevalence with select environmental factors for the centers with 13- to 14-year-olds. All models were adjusted for center mean exposure of interest, as well as the center and country mean population density, country gross national income per capita, and climate type. (*Created from values presented in Table 3 in Fuertes E, Butland BK, Anderson HR, et al. Childhood intermittent and persistent rhinitis prevalence and climate and vegetation: a global ecologic analysis. Ann Allergy Asthma Immunol 2014;113:386-392.e9. Note: effect estimates in original table are presented per one unit increase whereas effect estimates in the current figure are presented per one interquartile range increase.*)

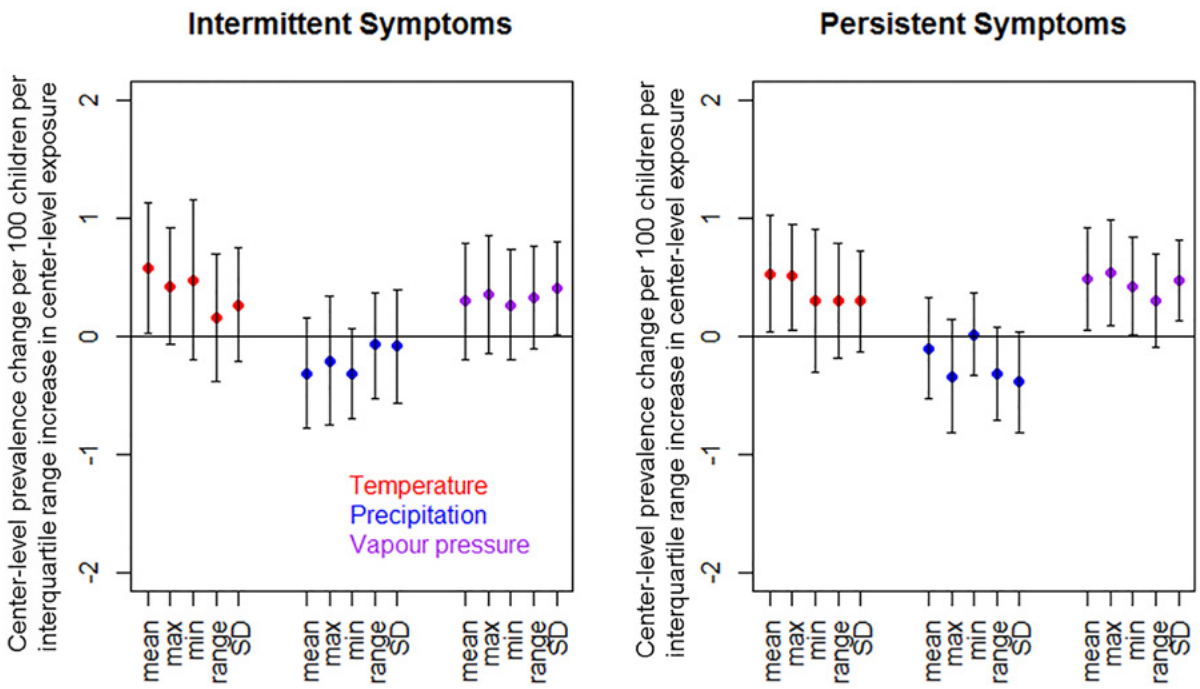

Figure 3 Within-country associations for intermittent and persistent rhinitis prevalence with select environmental factors for the centers with 13- to 14-year-olds. All models were adjusted for country mean exposure of interest, as well as the center and country mean population density, country gross national income per capita, and climate type. (*Created from values presented in Table 4 in Fuertes E, Butland BK, Anderson HR, et al. Childhood intermittent and persistent rhinitis prevalence and climate and vegetation: a global ecologic analysis. Ann Allergy Asthma Immunol 2014;113:386-392. e9. Note: effect estimates in original table are presented per one unit increase whereas effect estimates in the current figure are presented per one interquartile range increase.*)

Although not conclusive, this ecological study represents a first step in investigating how future changes in climate change may affect rhinitis symptom prevalence on a global scale.

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16 ENVIRONMENTAL RISK FACTORS FOR ALLERGIC RHINITIS – HOME ENVIRONMENT

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KEY MESSAGES

- Allergens from house dust mites and furry pet allergens is ubiquitous in homes and furry pet allergens can be transported by clothes and hair from other indoor environments. Cockroach allergens can be an important risk factors for allergic rhinitis (AR) in some parts of the world
- Cleaning and other hygienic measures can reduce allergen exposure but it is more unclear if they reduce allergic symptoms
- Dampness and indoor mould growth are well-established risk factors for AR, but the causative factors are not clearly identified and can differ between different climate zones
- Chemical emissions from recent redecoration and new building materials can be a risk factor for AR but the mechanisms are not well understood
- A sufficient ventilation flow in homes is important to reduce the exposure to particles and volatile organic compounds and to reduce the risk for building dampness and indoor mould growth

Allergic rhinitis (AR) occurs when an allergen triggers nasal symptoms in a sensitized individual, while non-allergic rhinitis (NAR) is triggered by non-allergic and non-infectious agents. In epidemiological studies, it is often difficult to distinguish between these two types of rhinitis and moreover non-allergic indoor factors can act as adjuvant factors for AR. House dust mites (HDM) allergy is a common cause of allergic asthma and AR, affecting 65-130 million persons globally, but the translation of the silent sensitization into symptomatic disease is still not well understood. Allergen sources are common in the home environment, including furry pets (cat and dogs), rats and mice, cockroaches, house dust mites, tropical storage mite (*Bloomia tropicalis*), fungal allergens (e.g. from *Penicillium sp*, *Cladosporium sp*. and *Alternaria sp*.) and allergenic pot plants (e.g. *Ficus benjamina* and *Yucca elephantipes*) (Table 1). Non-allergic factors includes particle pollutants (PM10 and PM2.5), environmental tobacco smoke (ETS), formaldehyde, volatile organic compounds (VOC) from new building materials and consumer products (Table 1 and Figure 1).

Building dampness and mould growth on indoor surfaces or in the construction are common in homes and could cause rhinitis in children and adults. Recently large studies in children and adults on AR have been published, e.g. from Asia. Presence of cockroaches was associated with AR in studies from China and France and with current rhinitis in China. In studies from China and Korea, recent redecoration and moving to a new home was associated with AR. However, one study from France found that new particle board in the home, a well-known source of formaldehyde emissions, was associated only with NAR. Windowpane condensation in wintertime is an indicator of a combination of poor ventilation and high air humidity and has been associated with AR in China and Sweden. Finally, daily cleaning of the homes was associated with a lower prevalence of AR in China.

The indoor environment in homes is complex and contains a large number of allergens and non-al-

TABLE 1

Common sources of indoor pollution in the home environment	
Allergenic source	**Main allergens**
Cats	Der p 1
Dogs	Can f 1
Horse	Ecu cx
Rats/mice	Mus m 1, Rat n 1
House dust mites (HDM)	Der p 1, Der f 1, Der m 1
Tropical storage mite (*Bloomia tropicalis*)	Blo t
Cockroaches	Per a 1, Bla g 1
Mould (e.g. *Penicillium sp. Cladosporium sp, Alternaria sp.*)	various allergens
Pot plants (e.g. *Ficus benjamina*, *Yucca elephantipes*, *Dieffenbachia picta* and *Euphorbia pulcherrima*)	various allergens
Other indoor factors	**Type of emissions**
New building materials	formaldehyde, various VOC
New chip board	formaldehyde
Environmental tobacco smoke (ETS)	nicotin, aldehydes, particles, VOC
Biomass and wood combustion	aldehydes, particles, VOC
Low ventilation flow (poor ventilation)	Increased levels of all pollutants
Building dampness	aldehydes, VOC, microbial VOC (MVOC), mycotoxins, endotoxin, mould, bacteria, microbial compounds

Figure 1 The complexity of the indoor environment in homes.

lergenic factors that can affect AR. Use of low-emission building materials and consumer products, reduction of tobacco smoke and other indoor combustion sources and sufficient air exchange is important, as well as sufficient cleaning. Moreover it is important to construct and maintain buildings in such a way that building dampness and indoor microbial growth is avoided to reduce the risk for AR.

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17 ENVIRONMENTAL RISK FACTORS FOR ALLERGIC RHINITIS - WORK ENVIRONMENT

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KEY MESSAGES

- Sensitizers (HMW and LMW allergens) and irritants may lead to occupational rhinitis (OR). There is an overlap between the different categories of eliciting agents. Sensitizers may also have irritating properties. Irritants may lead to new onset OR, but also to worsening of pre-existing disease
- The level of exposure, atopy and smoking are considered as the main potential determinants for the development of OR
- OR is a risk factor for the development of asthma. Work-related ocular-nasal symptoms are also a strong predictor of work exacerbated asthma
- Occupational exposures may also be involved in more severe forms of chronic rhinosinusitis

OCCUPATIONAL AND WORK-EXACERBATED RHINITIS

Environmental agents at the work place may lead to work-related rhinitis. Work-related rhinitis can be caused by work - occupational rhinitis (OR) – or exacerbated by work (work-exacerbated rhinitis). OR can be divided into allergic and non-allergic OR.

In general, allergic OR is characterized by a latency period i.e. a period between the start of exposure and the onset of symptoms whereas non-allergic OR might develop shortly after exposure (figure 1). Sensitizing agents - in most cases high molecular weight (HMW) allergens and sometimes low molecular weight (LMW) allergens – may induce an IgE mediated allergic reaction, responsible for allergic OR. Less frequently, single or multiple exposures to irritants will lead to non-allergic irritant-induced OR. Corrosive rhinitis is considered as the most severe form of irritant induced OR, characterized by persistent inflammation. Ulcerations and perforation of the nasal septum may be attributed to OR, but are more frequently seen in the context of cocaine sniffing and/or nose picking.

Apart from these occupational diseases caused by work, environmental stimuli at work may also lead to worsening of pre-existent rhinitis.

There is some overlap between the different categories of eliciting agents. Sensitizers may also have irritating properties. Irritants may lead to OR, but also to worsening of pre-existing rhinitis. Table 1 shows some examples of allergens and the corresponding occupations responsible for OR. The level of exposure, atopy and smoking are considered as the main potential determinants for the development of OR.

CHRONIC RHINOSINISITIS

Recent studies provide evidence that occupational exposures may also be involved in more severe forms of chronic rhinosinusitis (CRS). Exposures at work appear to be a risk factor for the occurrence, recurrence and persistence of CRS. Moreover, patients with job exposures appear to be less satisfied with the outcome of surgical procedures.

WORK RELATED RHINITIS AND ASTHMA

There is a close relationship between the presence of OR and the development of occupational asthma (OA). It has been esti-

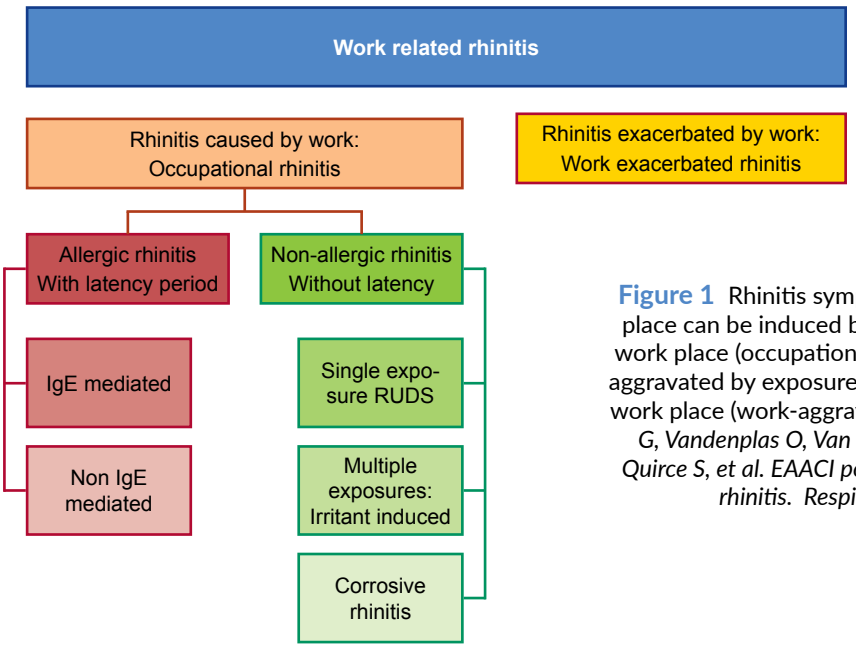

Figure 1 Rhinitis symptoms occurring in the work place can be induced by substances present in the work place (occupational rhinitis) or preexisting and aggravated by exposure to substances present in the work place (work-aggravated rhinitis). (*From Moscato G, Vandenplas O, Van Wijk RG, Malo JL, Perfetti L, Quirce S, et al. EAACI position paper on occupational rhinitis. Respir Res 2009;10:16.*)

TABLE 1

type of exposure leading to work-related rhinitis

Agents	Occupation	Prevalence (%)
High molecular weight agents		
Laboratory animals	Laboratory workers	6–33
Other animal-derived allergens	Swine confinement workers	8–23
Insects & mites	Laboratory workers, farm workers	2–60
Grain dust	Grain elevators	28–64
Flour	Bakers	18–29
Latex	Hospital workers, textile factory	9–20
Other plant allergens	Tobacco, carpet, hot pepper, tea, coffee, cocoa, dried fruit and saffron workers	5–36
Biological enzymes	Pharmaceutical & detergent industries	3–87
Fish and seafood protein	Trout, prawn, shrimp, crab & clam workers; aquarists & fish-food factory workers	5–24
Low molecular weight agents		
Diisocyanates	Painters, urethane mould workers	36–42
Anhydrides	Epoxy resin production, chemical workers, electric condenser workers	10–48
Wood dust	Carpentry & furniture making	10–36
Metals (*platinum*)	Platinum refinery	43
Drugs (*psyllium, spiramycin, piperacillin*)	Health care & pharmaceutical workers	9–41
Chemicals	Reactive dye, synthetic fibre, cotton, persulphate, hairdressing, pulp & paper, shoe manufacturing	3–30

Data from Moscato G, Vandenplas O, Van Wijk RG, Malo JL, Perfetti L, Quirce S, et al. EAACI position paper on occupational rhinitis. Respir Res 2009;10:16.

mated that the relative risk of OA amounts to 4.8 in workers with OR. Vice versa OR can be found in three-quarters of the patients with OA. Work-related ocular-nasal symptoms are also a strong predictor of work -exacerbated asthma (OR 6.7; CI 2.4-19.1)

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18 ENVIRONMENTAL RISK FACTORS FOR ALLERGIC RHINITIS - INDOOR AND OUTDOOR POLLUTION

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KEY MESSAGES

- Diesel-burning engines emit particulate matter which has been demonstrated to cause and aggravate asthma and enhance allergic sensitization leading to allergic rhinitis (AR) in children living in close proximity to high-traffic areas
- Volatile organic compounds are derived from chemical or microbial sources and at high levels can cause mucous membrane irritation resulting in non-specific upper respiratory symptoms as well as fatigue, and difficulty concentrating
- Solid biomass fuels are also a major source of indoor air pollution especially in underdeveloped countries dependent on this energy for heating and cooking
- Polyaromatic hydrocarbons from residential heating and gas appliances can impact the immunologic development of newborns and increase the number and duration of respiratory episodes in infants with prenatal exposure

OUTDOOR POLLUTION

Air pollution and global warming have significant health and economic effects on society. Outdoor pollution includes gases such as sulfur dioxide, ozone, nitrogen species, carbon monoxide, and particulate matter (PM) (coarse PM_{10}, fine $PM_{2.5}$, and ultrafine) and may contribute to the rising prevalence of allergic rhinitis (AR) and asthma in westernized countries (Table I). Air pollutants can be classified as primary/secondary, indoor/outdoor and as gaseous particulate (Table II). Studies have found that increased outdoor CO_2 levels combined with increased temperatures cause ragweed plants to grow larger and produce increased pollen. Diesel-burning engines emit PM which has been demonstrated to cause and aggravate asthma and enhance allergic sensitization in children living in close proximity to high-traffic areas. Ozone, a byproduct of diesel exhaust, can increase inflammation in the airways of asthma patients. A study of school-aged children in Germany found an association with atopy but only in children living in homes exposed to air pollution from high motor vehicle traffic and environmental tobacco smoke. A longitudinal study evaluated the effect of air pollution in causing atopy and asthma based on the child's geographic location over seven years using exposure modeling and found that $PM_{2.5}$ was associated with asthma, whereas nitrogen dioxide was associated with eczema, and living a distance less than 50 m to the nearest road was associated with asthma symptoms. In addition, another similar longitudinal study found that diesel exhaust particles (DEP) exposure enhances the risk of early aeroallergen sensitization and was associated with allergic rhinitis at 4 years of age.

INDOOR POLLUTION

Examples of indoor pollution include cigarette smoke, carbon monoxide, carbon dioxide, and volatile organic compounds (VOCs) (Table 2). VOCs are derived from chemical or microbial sources. Chemical VOCs include ketones and aldehydes like formaldehyde which emanate from building materials including adhesives, carpet, cleaners, linoleum, furniture, paint, printers, textiles, personal care

TABLE 1

National Ambient Air Quality Standards (adapted from http://www.epa.gov/air/criteria.html) *			
Pollutant	**Primary standards**	**Averaging times**	**Secondary standards**
CO	9 ppm (10 mg/m^3)	8-Hour †	None
	35 ppm (40 mg/m^3)	1-Hour †	None
NO_2	0.053 ppm (100 µg/m^3)	Annual (arithmetic mean)	Same as primary
PM_{10}	Revoked‡	Annual ‡ (arithmetic mean)	Revoked‡
	150 µg/m^3	24-Hour §	Same as primary
PM2.5	15.0 µg/m^3	Annual ‖ (arithmetic mean)	Same as primary
	35 µg/m^3	24-Hour ¶	Same as primary
O_3	0.08 ppm	8-Hour #	Same as primary
	0.12 ppm	1-Hour** (applies only in limited areas)	Same as primary
Sulfur oxides	0.03 ppm	Annual (arithmetic mean)	—
	0.14 ppm	24-hour †	—
	—	3-hour †	0.5 ppm (1300 µg/m^3)

** Primary standards, limits set to protect public health, especially sensitive subpopulations such as patients with asthma, the elderly, and children. Secondary standards, limits set to protect public welfare such as visibility and damage to crops, animals, and buildings. Levels for VOCs have not been established.*

†Not to be exceeded more than once per year.

‡Because of a lack of evidence linking health problems to long-term exposure to coarse particle pollution, the agency revoked the annual PM10 standard in 2006 (effective December 17, 2006).

§Not to be exceeded more than once per year on average over a period of 3 years.

‖To attain this standard, the 3-year average of the weighted annual mean PM2.5 concentrations from single or multiple community-oriented monitors must not exceed 15.0 µg/m^3.

¶To attain this standard, the 3-year average of the 98th percentile of 24-hour concentrations at each population-oriented monitor within an area must not exceed 35 µg/m^3 (effective December 17, 2006).

#To attain this standard, the 3-year average of the fourth-highest daily maximum 8-hour average O3 concentrations measured at each monitor within an area over each year must not exceed 0.08 ppm.

*** (1) The standard is attained when the expected number of days per calendar year with maximum hourly average concentrations above 0.12 ppm is ≤1. (2) As of June 15, 2005, the Environmental Protection Agency revoked the 1-hour O_3 standard in all areas except the fourteen 8-hour O_3 nonattainment Early Action Compact (EAC) areas.*

products, and chemically treated clothing. High VOC levels (> 3000 µg/m^3) can cause mucous membrane irritation resulting in non-specific upper respiratory symptoms as well as fatigue, and difficulty concentrating.

Use of solid biomass fuels is also a major source of indoor air pollution. This is especially true in underdeveloped countries where heating and cooking depends on these biomass fuels and when combined with poor ventilation results in repeated periods of emissions that have been associated with increased childhood respiratory infections and development of chronic obstructive pulmonary disease, asthma, and malignancy.

Studies have also investigated the health effects of air pollution during pregnancy and found that moderate- to long-term high air pollution exposure can alter T-cell production in neonates. Polyaromatic hydrocarbons (PAHs), emitted from residential heating and gas appliances, may also impact the immunologic development of newborns. Studies have found that the number and duration of respiratory episodes were greater in infants exposed prenatally to higher levels of PAHs.

In summary, there is overwhelming evidence to support the health effects of air pollution on respiratory health. However, many questions remain unanswered which require further investigation.

TABLE 2

Classification of air pollutants
A. Primary-secondary pollutants
(i) Primary: pollutants emitted directly into the atmosphere (eg, SO2, some NO_x species, CO, PM)
(ii) Secondary: pollutants that form in the air as a result of chemical reactions with other pollutants and gases (eg, ozone, NO_x, and some particulates)
B. Indoor-outdoor pollutants
(i) Indoor pollutants
(a) Sources: cooking and combustion, particle resuspension, building materials, air conditioning, consumer products, smoking, heating, biologic agents
(b) Products: Combustion products (eg, tobacco and wood smoke), CO, CO_2, SVOC (eg, aldehydes, alcohols, alkanes, and ketones), microbial agents and organic dusts, radon, manmade vitreous fibers
(ii) Outdoor pollutants
(a) Sources: industrial, commercial, mobile, urban, regional, agricultural, natural
(b) Products: SO_2, ozone, NOx, CO, PM, SVOC
C. Gaseous-particulate pollutants
(i) Gaseous: SO_2, NOx, ozone, CO, SVOC (eg, PAH, dioxins, benzene, aldehydes, 1,3-butadiene)
(ii) Particulate: coarse PM (2.5-10 µm; regulatory standard = PM_{10}), fine PM (0.1-2.5 µm; regulatory standard = $PM_{2.5}$); ultrafine PM (<0.1 µm; not regulated)

NOx, Nitrogen oxides; SVOC, specific volatile organic compounds.

(Data from J Allergy Clin Immunol, 114/5, Bernstein JA, Alexis N, Barnes C, Bernstein IL, Bernstein JA, Nel A, Peden D, Diaz-Sanchez D, Tarlo SM, Williams PB. Health effects of air pollution, 1116-1123, Copyright 2004, with permission from Elsevier.)

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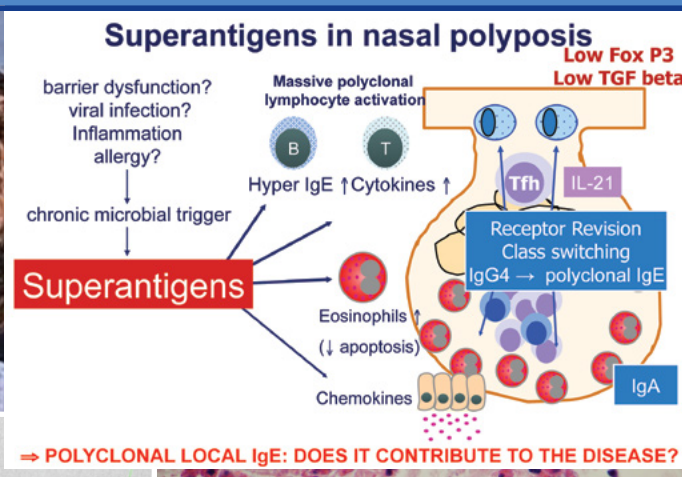
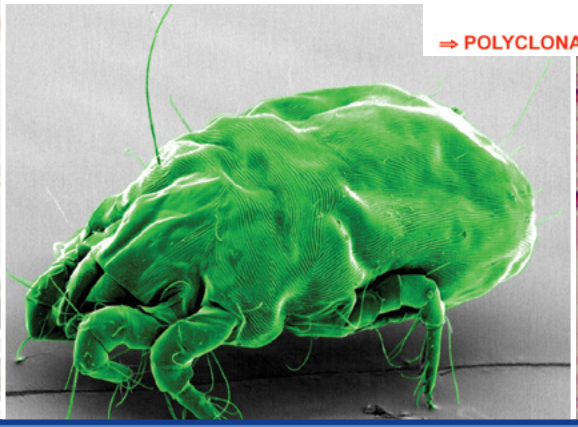
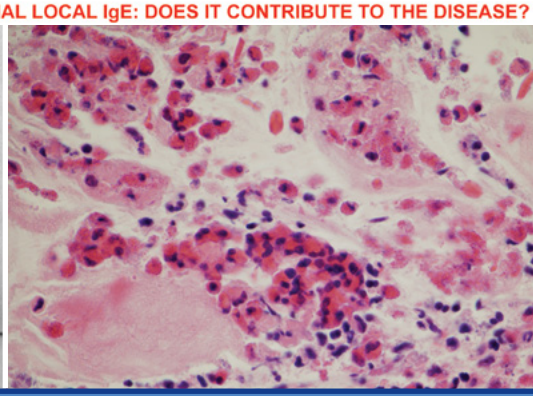
Section C







ALLERGIC RHINITIS

CLINICAL FEATURES AND CO-MORBIDITIES

* Clinical features of allergic rhinitis
* Triggers of allergic rhinitis: inhalant allergens
* Triggers of allergic rhinitis – cross-reactive allergens
* Triggers of allergic rhinitis - work-related allergens
* Co-morbidities of allergic rhinitis: nasal polyposis
* Co-morbidities of allergic rhinitis: ocular allergy
* Co-morbidities of allergic rhinitis: eosinophilic otitis media
* Co-morbidities of allergic rhinitis: eosinophilic esophagitis
* The united airway disease
* Atopic dermatitis and allergic rhinitis: Where is the evidence for comorbidity?
* Allergic rhinitis and food allergy
* The link between the skin and the airways
* Allergic rhinitis and angioedema
* Allergic rhinitis and sleep apnea

1 CLINICAL FEATURES OF ALLERGIC RHINITIS

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KEY MESSAGES

- Common symptoms of allergic rhinitis involve the nose and extend beyond to affect the eyes, ears, sinuses, and lungs
- Nasal symptoms include nasal itching and congestion, runny nose, and paroxysmal sneezing
- Additional symptoms include ear fullness, itching and tearful eyes, post-nasal drip, and cough
- Classic physical exam findings include swollen nasal turbinates, pale nasal cavity lining, and cobblestoning

While allergic rhinitis (AR) refers to an inflammatory process of the nasal passages, symptoms involve the nose and may extend beyond to affect the eyes, ears, sinuses, and lungs. Commonly reported nasal symptoms include nasal itching and congestion, runny nose, and sneezing. Patients may also complain of ear symptoms including ear fullness and popping. Often AR will involve the conjunctiva and as such patients may experience itching, burning, or tearful eyes. Other frequently associated symptoms are throat itching and post-nasal drip.

Severe persistent AR may lead to snoring, mouth breathing, and sinus pressure symptoms. With chronic symptoms, children may often sniff, snort, and repeatedly clear their throats. While scratching their itchy palates, children may also make a clicking sound called the "palatal click." Table 1 provides an overview of common clinical features of AR.

AR is often associated with classic physical findings as well. On nasal examination, the nasal cavity lining will often appear pale or have a bluish hue in contrast to its normal pinkish hue. Nasal turbinates may be enlarged and swollen. Clear nasal discharge may also be seen (Figure 1). Patients may also have "cobblestoning" on exam, which refers to the cobblestone-like or bumps often seen in the back of the throat.

Other physical features include lines below the lower eyelid referred to as Dennie-Morgan lines. Patients may have dark circles around the eyes referred to as allergic shiners (Figure 2). In ad-

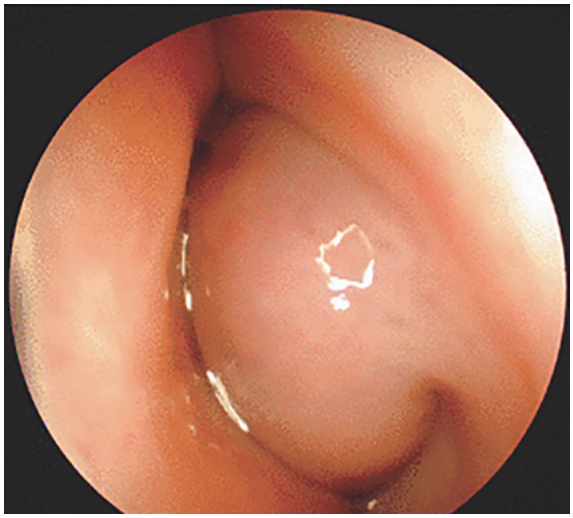

Figure 1 Typical nasal exam findings of allergic rhinitis with clear nasal drainage and swollen inferior turbinate. (*From Onerci TM. Rhinitis. Diagnosis in Otorhinolaryngology. 2010; pp 60-64.*)

TABLE 1

Clinical features of allergic rhinitis	
System	**Symptoms**
Nose	Sneezing, runny nose, and nasal congestion
Ears	Tearful, burning, and itching eyes
Ears	Ear popping and fullness
Sinus	Pressure over the cheeks and forehead
Throat	Itchy throat and post nasal drip
Lungs	Cough and symptoms of asthma

Figure 2 Pediatric patient with allergic rhinitis demonstrating "allergic shiners" and mouth breathing (source UptoDate)

Figure 3 The Allergic Salute. (*From Marks M: Physical Signs of Allergy of the Respiratory Tract in Children. New York, American College of Allergy, Asthma and Immunology, 1990.*)

dition, children will often perform the "allergic salute," a rubbing motion performed by using the palm of their hand to relieve their nasal itching (Figure 3). Over time, this can lead to a transverse crease along the nose.

Symptoms of AR are caused by an allergic reaction to allergens in the air. Depending on the allergen, symptoms may occur seasonally or year round. Common seasonal allergens include grasses, trees, weeds, and molds. Common year round or perennial allergens include animal dander, molds, and dust mites. While seasonal allergic rhinitis tends to predominate in children and perennial in adults, individuals can have both types.

AR is a global health problem. In addition to appropriate treatment, symptom recognition is important in managing and reducing morbidity in this increasingly prevalent disease.

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2a TRIGGERS OF ALLERGIC RHINITIS: INHALANT ALLERGENS

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INTRODUCTION

Inhalant allergens are plant and animal derived proteins that have the capacity to generate IgE responses and allergic disease in susceptible individuals. Sensitization to inhalant allergens is the main risk factor for allergic rhinitis (AR), asthma and allergic conjunctivitis. In addition to the adaptive IgE immune response, many allergens engage adaptive immune responses via proteolytic actions to destroy protective mucous layers in the airways or activate the protease activate receptor PAR2 to contribute to epithelial inflammation.

CLASSIFICATION

Inhalant allergens were traditionally classified as seasonal or perennial, however the allergic rhinitis and its impact on asthma (ARIA) report has suggested a classification that relates to the duration of impact than an allergen has on allergic disease. For example grass pollen can be seasonal in a temperate region, but causes perennial disease in the tropics and sub-tropics. The preferred nomenclature for inhalant allergens is intermittent and persistent.

KEY MESSAGES

- Inhalant allergens are plant and animal derived proteins that have the capacity to generate IgE responses and allergic disease in susceptible individuals; they cause rhinitis, conjunctivitis,
- asthma and atopic dermatitis
- The preferred nomenclature for inhalant allergens is intermittent and persistent
- The diagnosis of inhalant allergy requires the presence of sensitization and timing of disease to exposure to the inhalant allergens

HOUSE DUST MITES

Two common mites from the *Dermatophagoides* (Latin for 'skin eater') genus can cause allergic disease: the European house dust mite (HDM) (*Dermatophagoides pteronyssinus*) (Figure 1) and the American HDM (*Dermatophagoides farinae*); however these are not confined to their geographic titles and are present worldwide. In tropical regions, the tropical mite *Blomia tropicalis* is the major mite allergen. Der P1, a cysteine protease is the most characterised, and is a digestive enzyme that is excreted in mite faeces. Mites inhabit and thrive in conditions where there is skin and humidity, particularly bedding, but may inhabit furniture and carpet. Pillows can contain up to 2000 mites per gram of dust. Dust mites require moulds for digestion. In their life cycle, mites can lay about 70 eggs and produce 2000 allergenic faecal particles. Most mite reduction trials have methodological issues and a Cochrane review summarised that extensive bedroom-based environmental control measures **may** be of use in reducing perennial rhinitis symptoms.

POLLENS

Pollens are the male spores of plant seeds from trees, grasses and weeds. Pollen grains have a sturdy outer shell and inner spores. As plants have evolved, pollens have developed a more complex outer structure (Figures 2 & 3). Tree pollens (e.g, birch, elm, olive, acacia, ash, cedar, pine) have a shorter and earlier duration of pollination and

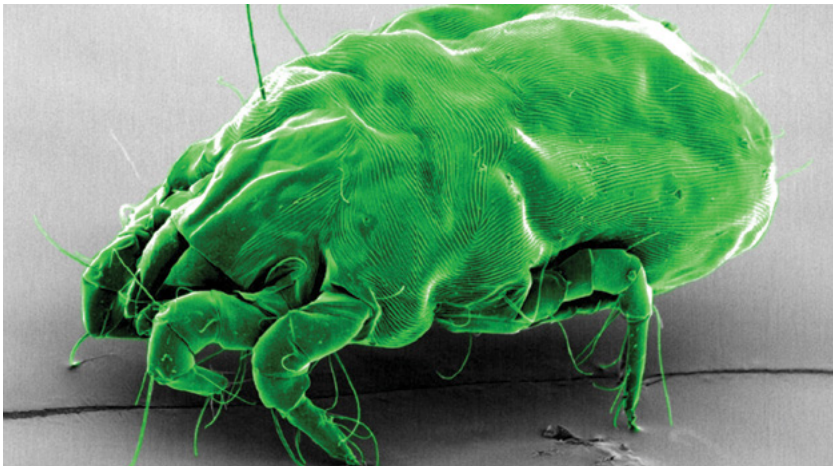

Figure 1 Scanning electron microscopy (false colour) of the common house dust mite. *Dermatophagoides pteronyssinus*.

Figure 2 Scanning electron microscopy (false colour) of Bermuda grass *Cynodon dactylon*.

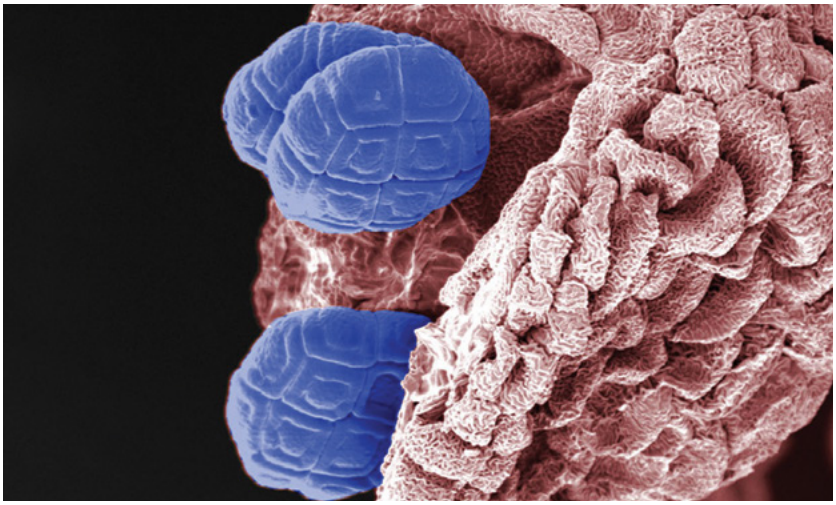

Figure 3 Scanning electron microscopy (false colour) demonstrating a complex sulci (furrow) pattern of acacia pollen grains.

may release pollen for only a few weeks in spring. Grasses (e.g. Rye, Timothy, Orchard, Bermuda) have late spring and summer peaks and weeds (Ragweed/Ambrosia, Plantain, Sorrel) follow a similar release pattern, but also continue pollen release into autumn. In temperate zones weeds generally cease pollen release with the first freeze. Pollens can travel for miles, although some pollens (e.g. plantain and birch) are quite heavy and are not widely dispersed. Grass pollen release is increased 8-20 fold with the atmospheric changes of thunderstorms.

MOULD

Moulds are the major component found in environmental allergen traps. They thrive and reproduce in moist, dark environments such as dirt, wood, food, plant matter and animal matter. Common inhalant allergen species include, *Alternaria*, *Aspergillus*, *Helminthosporium*, *Cladosporium* and *Penicillium*. Inhalant allergic disease has been associated with fungal dermatophytes including T*richophyton spp*, *Candida albicans* and *Epidermophyton*. Most fungi have branching threads (hyphae, Figure 4). A mycelium is a cluster of hyphae. In addition to allergic disease several moulds (e.g. aspergillus) cause invasive disease and are capable of producing volatile organic compounds that cause airway irritation. Moulds are regarded as persistent allergens however spore release can increase dramatically with thunderstorms to produce an intermittent clinical disease pattern.

DANDER

Domestic cats and dogs are the most characterized pet allergens, although dander from a wide range of animals may cause inhalant allergic disease. The most important cat allergens are the glycoproteins Fel d1 (from sebaceous glands)

and Fel d4 (in saliva). Cat allergens are very pervasive and resistant to elimination measures. Dog hair and saliva can provoke allergic symptoms in sensitised individuals.

OTHER INHALANT ALLERGENS

A wide range of biological materials including feathers, insect materials (e.g. cockroach, housefly) and latex can provoke inhalant allergic disease.

DIAGNOSIS OF ALLERGY

The clinical diagnosis of allergic disease requires symptomatology in the presence of the allergen and the presence of IgE on testing (skin prick, RAST and/or provocation). Pollen maps (Figure 5) can be helpful when correlating disease with positive tests. Clinical disease caused by inhalant allergens can be enhanced by the presence of high ozone levels and pollutants including smoke and diesel exhaust particles.

Figure 4 Light Microscopy of *Alternaria alternata* showing branched acropetal chains and multicelled, conidia with short conical beaks.

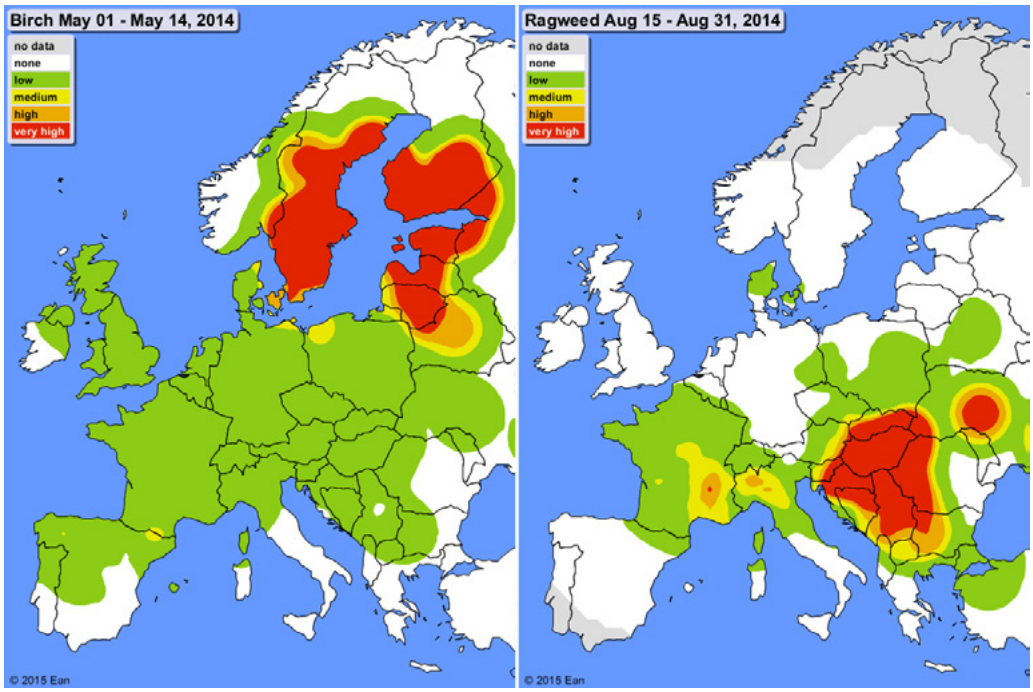

Figure 5 European pollen map of birch (*Betulla* pendula in early May and ragweed (*Ambrosia artemisiifolia*) in mid-end August (Code: white nil, green low, yellow moderate, orange high and red very high) Image courtesy of EAN (European Aeroallergen Network) Medical University Vienna, Austria.

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2b TRIGGERS OF ALLERGIC RHINITIS – CROSS-REACTIVE ALLERGENS

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KEY MESSAGES

- Cross-reactivity is common in allergic rhinitis
- Cross-reactivity allows simplification of diagnostic and therapeutic strategies
- Taxonomic family-specific marker allergens help identifying the source of primary sensitization
- Pan-allergens can assist in excluding primary sensitization

Allergic rhinitis (AR) is a disease triggered by the interaction between mast cell-bound specific IgE antibodies and inhaled allergens. The most common triggers are house dust mites, and grass, tree and weed pollen. In all cases, multiple species have been implicated, e.g. *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, and *Blomia tropicalis* for mites, a long list of grass species including *Phleum pratense*, *Lolium perenne* and *Poa pratensis*, various trees from the order of the *Fagales* to which the *Betulaceae* (birch, alder and hazel) and the *Juglandaceae* (walnut) families belong, and the order of the *Lamiales* with the family of the *Oleaceae* (olive and ash), and finally a variety of allergenic weeds such as the *Asteraceae* (mugwort and ragweed), the *Urticaceae* (*Parietaria judaica*), the *Plantaginaceae* (plantain) and the *Amaranthaceae* (Russian thistle). Depending on climatic and socio-economic characteristics of the domicile of a patient, the actual combined exposure to these potential triggers differs widely in composition.

Establishing the exact composition of exposure to the level of individual species is in fact impossible, e.g. because pollen of different species within plant families can hardly if at all be distinguished microscopically. Antibody responses as a read-out for exposure usually do not really give the answer either, because there is a high degree of antibody cross-reactivity between homologous allergens of different species of pollen or of house dust mites, within a family or even across family (or even order) boundaries.

The degree of cross-reactivity is correlated with the percentage of structural homology, which is determined by adjacency in the family tree (genealogical relationship). Both from a diagnostic and a therapeutic perspective it is important to be aware of cross-reactivity. Within a family, cross-reactivity is usually so extensive that both for diagnosis and for allergen immunotherapy (AIT), a single high IgE-binding species is sufficient, e.g. *Pheum pratense* for grass pollen, *Betula verrucosa* for the birch family, or *Dermatophagoides pteronyssinus* for mites. There is no convincing evidence that patients are selectively allergic to just one species of grass or tree pollen or one species of mites. A mix of allergen extracts for diagnosis or AIT may seem more comprehensive but in fact only complicates production and standardization.

Cross-reactivity outside genealogical families caused by so-called pan-allergens may lead to confusion about the primary source of sensitization. For pollen, profilins and cross-reactive carbohydrate determinants (CCD), and for arthropods tropomyosins are responsible for such broader cross-reactivity. Molecular allergology now offers the opportunity to establish whether sensitization

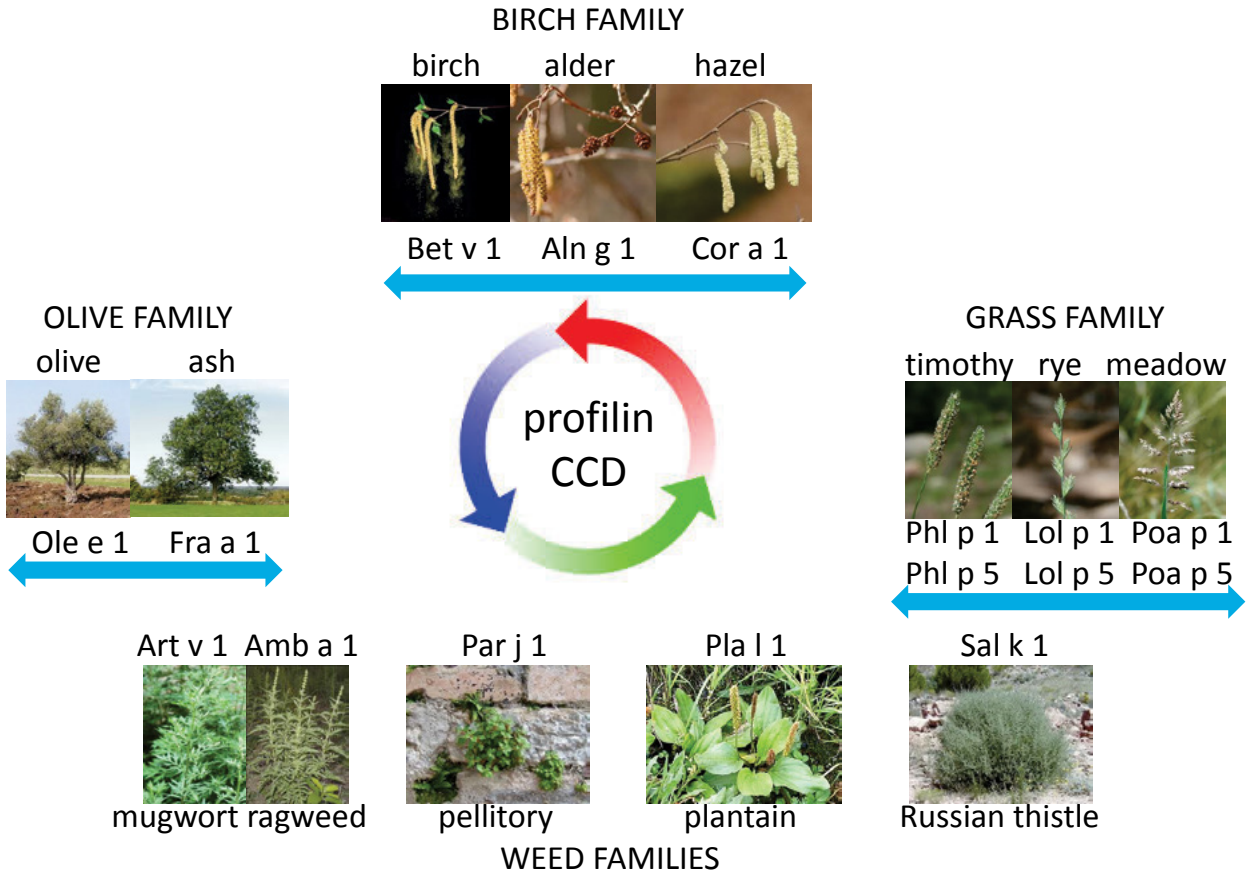

Figure 1 Cross-reactivities of most dominant allergenic pollen. Arrows indicate cross reactivity. The circular arrows imply that profilin and CCD are pan-allergens present in all pollen and cause cross-reactivity across family borders. The major allergens of the weeds essentially do not cross-react.

is the true primary sensitization or cross-reactivity that started with another primary sensitizer. For allergenically important genealogical families, marker allergens for primary sensitization have been identified (Table 1). If these are negative, and only pan-allergens are responsible for IgE reactivity, clinical relevance is unlikely and AIT not warranted.

TABLE 1

Marker allergens for primary sensitization to a member of a genealogical family		
House dust mite	*Dermatophagoides pteronyssinus*	Der p 1
	Dermatophagoides farinae	Der p 2
	Blomia tropicalis	Blo t 5
Grass pollen	*Gramineae or Poaceae*	Phl p 1, Phl p 5
Tree pollen	*Fagales*	Bet v 1
	Lamiales	Ole e 1
Mugwort pollen	*Artemisia vulgaris*	Art v 1
Ragweed pollen	*Ambrosia artemisifolia*	Amb a 1
Pellitory pollen	*Parietaria judaica*	Par j 1
Plantain pollen	*Plantago lanceolata*	Pla l 1
Russian thistle	*Salsola kali*	Sal k 1

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2c TRIGGERS OF ALLERGIC RHINITIS - WORK-RELATED ALLERGENS

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KEY MESSAGES

- Work-related rhinitis includes **occupational rhinitis** (OR), i.e. an inflammatory disease of the nose due to causes and conditions attributable to a particular work environment, and **work-exacerbated rhinitis**, that is pre-existing or concurrent rhinitis exacerbated by workplace exposures
- **Allergic** OR may be induced by high-molecular-weight (HMW) agents (i.e. glycoproteins from vegetal and animal origin) and by some low-molecular-weight (LMW) agents acting through an IgE-mediated mechanism, or can be induced by LMW-agents acting by non-IgE, immunological mechanisms
- **Non-allergic** OR is caused by the work environment through irritant, non-immunological mechanisms
- Simultaneous multiple exposure to irritants and sensitizers can also induce work-related rhinitis

Work-related rhinitis (WRR) includes **occupational rhinitis** (OR), that is an inflammatory disease of the nose due to causes and conditions attributable to a particular work environment, and **work-exacerbated rhinitis**, that is pre-existing or concurrent rhinitis exacerbated by workplace exposures (Figure 1).

OCCUPATIONAL RHINITIS

OR is the most frequent and recognised form of WRR and can be allergic, i.e. immunologically mediated, and non-allergic, i.e. mediated by irritant mechanisms.

Occupational exposures inducing allergic OR are the same as for occupational asthma. High-molecular-weight (HMW) agents such as glycoproteins from vegetal and animal origin (e.g. flours, latex, animal-derived allergens) and some low-molecular-weight (LMW) compounds (e.g. platinum salts, anhydrides) can cause allergic OR through an IgE-mediated mechanism. Some LMW agents, e.g. isocyanates, can act with non-IgE, cell-mediated immunological mechanisms, which have not yet been fully characterized. (Figure 2)

Non-allergic OR is caused by the work environment through irritant, non-immunological mechanisms. An acute form of irritant-induced OR occurring without a latency period, after a single exposure to high levels of irritants at work is called '**reactive upper airways dysfunction syndrome**' (RUDS). Exposure to volatile organic solvents and pesticides has been associated to the development of RUDS. Symptoms of rhinitis may also present in subjects repeatedly exposed at work to irritants (vapors, fumes, smokes, dusts), without any identifiable exposure to high concentration of irritants. This entity is recognized as **multiple exposure irritant-induced** OR. A variety of occupational exposures have been associated with this type of OR, including ozone, volatile organic compounds, fuel oil ash, grain and cotton dust, formaldehyde, chlorine, wood dust, thermal degradation products of polyurethanes, and waste handling. The term 'corrosive rhinitis' describes the most severe form of irritant-induced OR, which is characterized by permanent inflammation of the nasal mucosa, sometimes associated with ulcerations and perforation of the nasal septum, that may develop after

Figure 1 Classification of work related rhinitis. (*Modified from EAACI Task Force on Occupational Rhinitis, Moscato G, Vandenplas O, et al. Occupational Rhinitis. Allergy 2008;63:969-980.*)

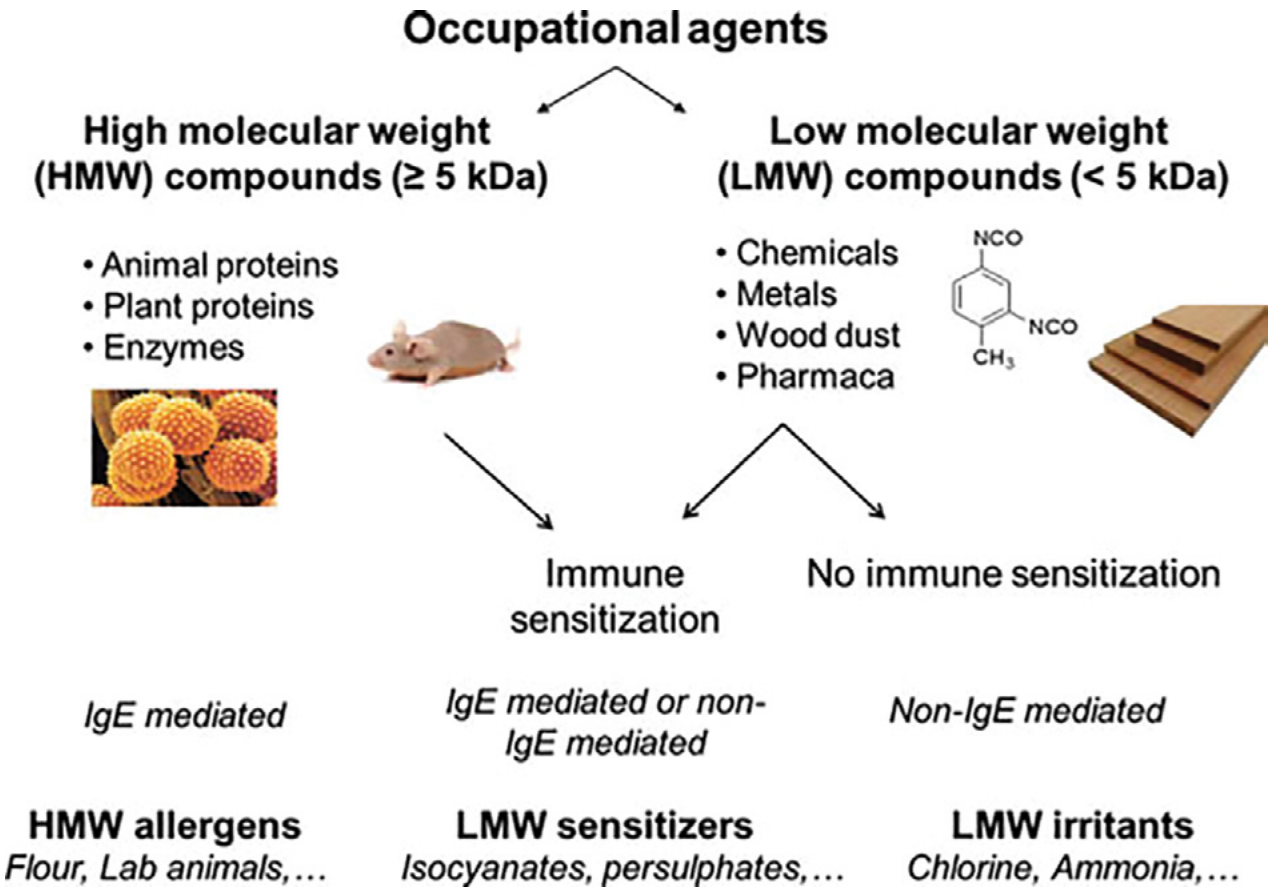

Figure 2 Occupational agents inducing occupational rhinitis according to their etiopathogenesis. (*Reproduced with permission from Hox V, Steelant B, Fokkens W, et al. Occupational upper airway disease: how work affects the nose. Allergy 2014;69:282-291, with permission from Willey Blackwell.*)

TABLE 1

Work-related rhinitis related to exposure to multiple agents	
Occupation	**Agents**
Cleaners	Various cleaning agents (Chlorine/bleach, dust)
Grape farmers	Various pesticides (Bipyrifyl herbicides -paraquat, diquat-, dithiocarbamate fungicides, carbamate insecticides)
Greenhouse workers	Inhalant allergens, endotoxins, pesticides
Construction painters	Paints
Automotive piston ring manufacturing workers	Metal working fluid aerosol (microbes, endotoxins, metals)

Modified from Siracusa A, Folletti I, Moscato G. Nonallergic work-related rhinitis. Review article. Curr Opin Allergy Clin Immunol 2013;13:159-166.

exposure to high concentrations of irritating and soluble chemicals like, for instance, chromium.

WORK-EXACERBATED RHINITIS

A wide variety of conditions at work, including irritant agents (e.g., chemicals, dusts, fumes), physical factors (e.g., temperature changes), emotions, second-hand smoke, and strong smells (e.g., perfumes) can trigger or worsen symptoms of a pre-existing or concurrent personal rhinitis.

EXPOSURE TO MULTIPLE AGENTS

A high prevalence of rhinitis in working populations that were simultaneously exposed to several potentially irritant and sensitizing agents, both LMW and HMW agents, has recently been reported (Table 1). Cleaners, farmers, greenhouse workers, construction painters, automotive piston ring manufacturing workers have been described.

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3a CO-MORBIDITIES OF ALLERGIC RHINITIS: NASAL POLYPOSIS

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KEY MESSAGES

- IgE is involved in both AR and CRSwNP, although in AR it is allergen-specific and in CRSwNP it is polyclonal
- It is not clear whether atopy contributes to the development of CRSwNP
- CRSwNP are often colonized with S. aureus and IgE to S aureus superantigens are related to disease severity
- Nasal polyps are frequently associated with (non-atopic, late onset) asthma and aspirin intolerance
- The treatment of nasal polyps is indispensable in the control of asthma

Allergic rhinitis (AR) and chronic rhinosinusitis with nasal polyps (CRSwNP) are both T helper 2 mediated inflammatory diseases of the nasal mucosa with high concentrations of IgE. AR affects 30 % of the population and allergen-specific IgE plays a well-known central role. CRSwNP affects 4% of the population and is frequently associated with late onset intrinsic asthma. IgE in AR is monoclonal allergen-specific and polyclonal in CRSwNP.. Although this polyclonal IgE is functional, it does not point to comorbid allergic disease. The prevalence of allergy in CRSwNP, diagnosed by skin prick tests, has been reported to vary from 10 to 54%.. Interestingly, allergen exposure in atopic nasal polyp (NP) patients does not clearly enhance disease expression, in contrast to patients with AR. The monoclonal IgE in AR reflects the allergic constitution. The polyclonal IgE in atopic NP patients however suppresses atopic symptoms. AR does probably not predispose to the development of NP, as their prevalence in the atopic population is similar to the general population, which in a French study was estimated 2,11% of the adult population. The treatment of NP is still problematic because there are no effective medical treatments available and because of a high recurrence rate after surgical NP removal. Anti-IgE treatment appears to be effective in both atopic and non-atopic patients with CRSwNP and comorbid asthma, suggesting this 'non-atopic' IgE plays a pivotal role in CRSwNP.

CRSwNP is frequently associated with late onset intrinsic asthma, and can be associated with aspirin intolerance. The triad CRSwNP, asthma and aspirin intolerance was termed Samter's triad and is actually known as aspirin-exacerbated respiratory disease.. NP in Samter's triad are typically recalcitrant and hard to treat, and asthma is likewise severe. Furthermore, asthma control is unlikely in uncontrolled CRSwNP. In contrast to AR associated asthma, co-morbid asthma in NP disease is mostly non-atopic and its onset is generally in the adult life. Thus, atopy cannot explain the presence of co-morbid asthma in NP patients. It is thought that many factors contribute in the pathogenesis of CRSwNP, including colonization with *Staphylococcus aureus*. Their enterotoxins can act as superantigens resulting in an immune response of increased magnitude and a massive IgE response (Figure 1). The overexpression of IgE and IL5, and the presence of SE-specific IgE in CRSwNP is associated with an increased risk of asthma (Figure 2).

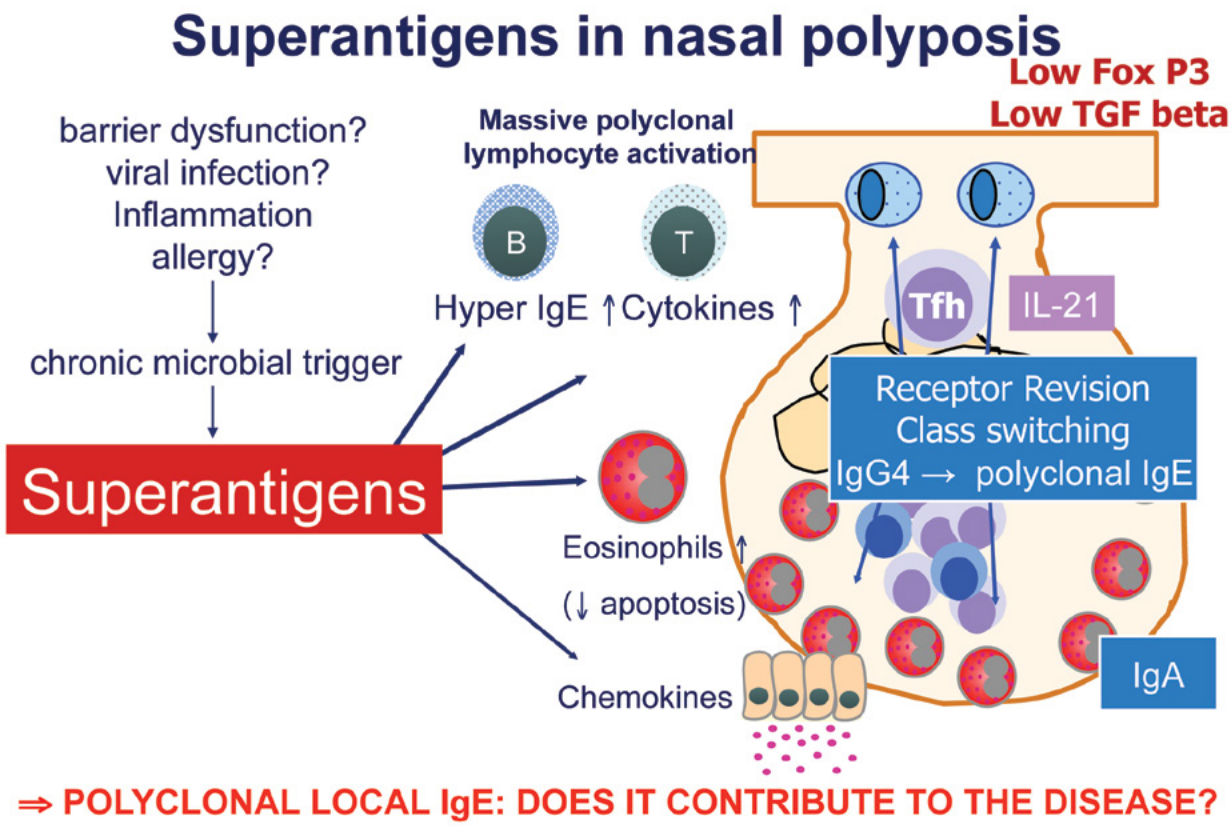

Figure 1 Enterotoxins derived from *Staphylococcus aureus* act as superantigens, resulting in high levels of polyclonal IgE.

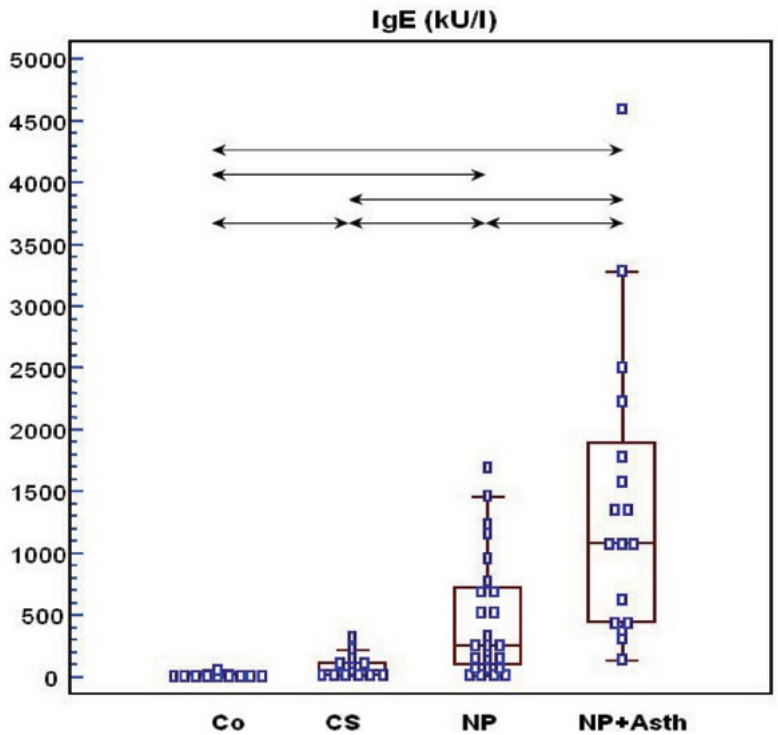

Figure 2 Higher levels of IgE are found in nasal polyp tissue when patients suffer from co-morbid asthma. Elevated local IgE seems to be a risk factor for asthma development in patients with nasal polyps.

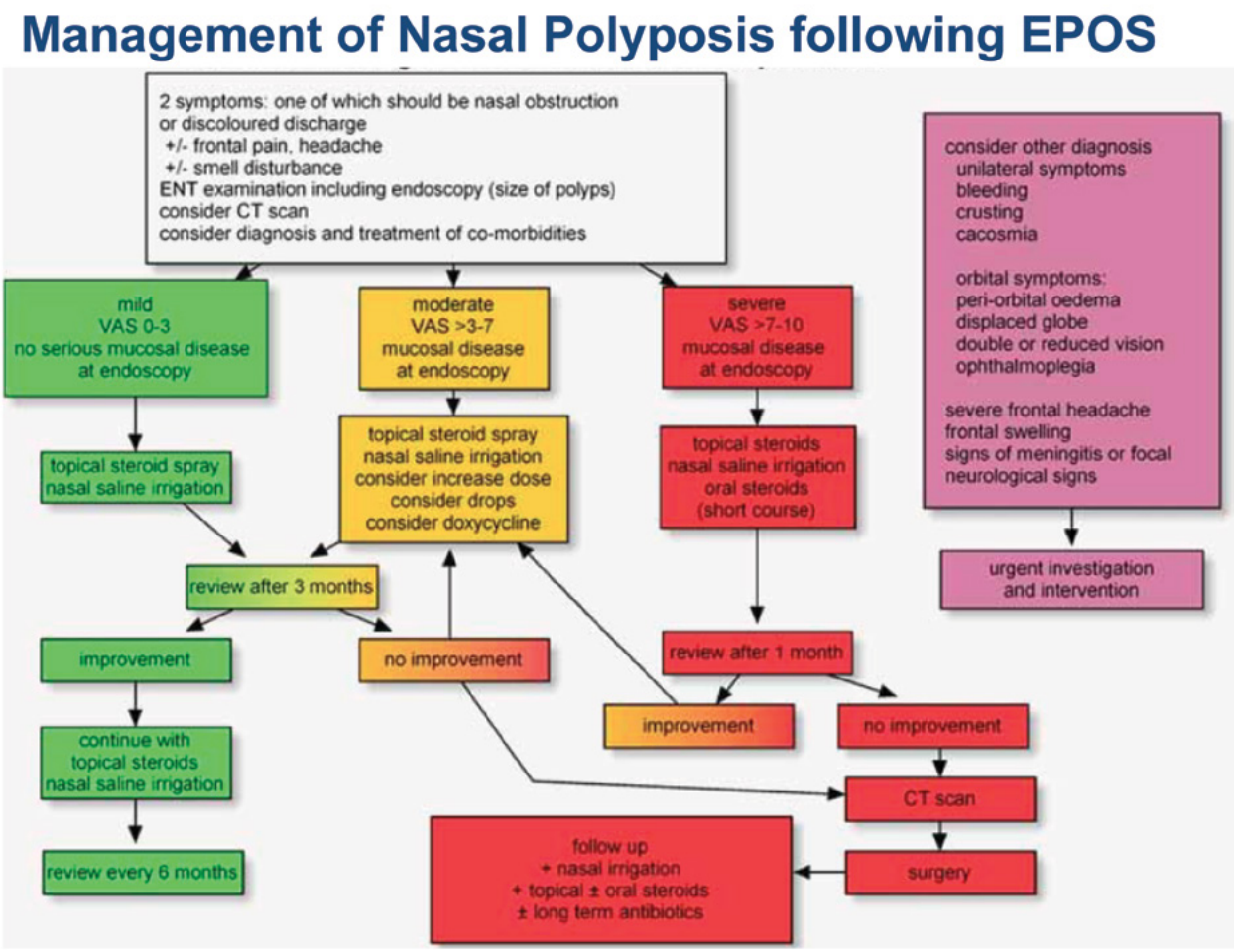

Figure 3 The evidence-based management scheme for nasal polyps in the adult population as described by the EPOS guidelines. (*From Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012;(23):3 p preceding table of contents, 1-298.*)

CRSwNP and asthma are associated with high morbidity and socio-economic cost. Control is essential in the prevention of exacerbations. Treatment of CRSwNP following the evidence-based EPOS management scheme (Figure 3) is indispensable to achieve control of co-morbid asthma. Recognition of aspirin intolerance in patients with CRSwNP is important to educate patients and to prevent life threatening responses.

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3b CO-MORBIDITIES OF ALLERGIC RHINITIS: OCULAR ALLERGY

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KEY MESSAGES

- Allergic conjunctivitis is one of the most common comorbidities of allergic diseases, especially of allergic rhinitis
- Allergic rhinoconjunctivitis can be seasonal or perennial
- Symptoms can considerably affect quality of life
- New therapeutic approaches are improving rhinoconjunctivitis management

Allergic rhinoconjunctivitis (ARC) is a very common manifestation of allergy affecting approximately 10-30% of adults and up to 40% of children. Allergic conjunctivitis (AC) is a comorbidity of other allergic diseases in more than 90% of cases. Specifically, in allergic rhinitis (AR) sufferers the prevalence of AC varies between 50-90 %. As noted by the Phase III ISAAC Study the prevalence of ARC in children is increasing worldwide and rises through childhood (8.5% at 6-7 years and 14.6% at 13-14 years). No significant gender differences have been described in the prevalence of ARC. AC can be seasonal (SAC) or perennial (PAC). SAC and PAC are the most common forms of ocular allergy.

AC is characterized by itching, hyperemia, watering and chemosis. Vision is not affected, but symptoms can be highly bothersome with a significant impact on productivity and quality of life. AC is related to both direct allergen contact with conjunctival mucosa as well as indirect contact via a nasal-ocular reflex. In SAC and PAC common environmental allergens lead to an inappropriate immunoglobulin E production and immunological sensitization. When subsequently exposed to the allergen, these antibodies can initiate mast cell degranulation and the entire allergic response. SAC and PAC involve an immediate (type I) hypersensitivity response. In SAC mast cells (MC) are the main infiltrating cells in the conjunctiva, with secreted products primarily orchestrating the inflammatory response. In PAC the inflammation is more chronic, with involvement of activated MC, eosinophils, neutrophils and some T cells.

SAC (Figure 1) occurs at the same time each year and recurs seasonally with the changes in pollens and allergens present. Symptoms tend to last a few weeks each year and may vary with the pollen count. Grass pollens tend to cause symptoms in early summer, usually from April through to July. Other pollens may cause symptoms as early as February or March or as late as September. PAC (Figure 2) persists throughout the year. It is most commonly due to an allergy to house dust mite. PAC is becoming more frequent that SAC, probably due to new perennial airborne allergens or irritants, such as pollutants.

Traditional therapy for SAC and PAC has been topical administration of antihistamines or mast cells stabilizers. In the last few years therapeutic approach has evolved toward more specific therapies (allergen immunotherapy, topical immunosuppressants) improving its management, especially for severe cases.

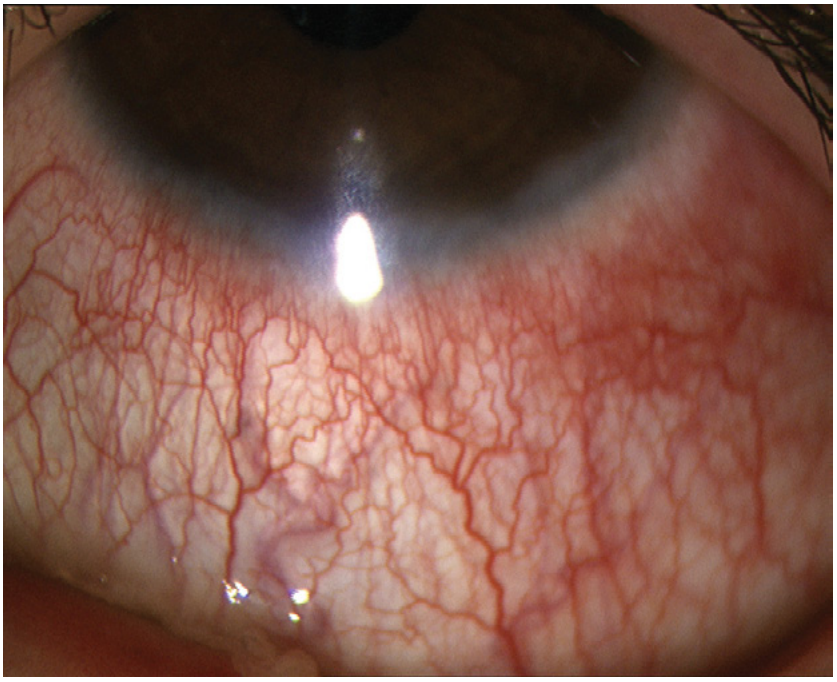

Figure 1 Acute seasonal allergic conjunctivitis

Figure 2 Perennial allergic conjunctivitis

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3c

CO-MORBIDITIES OF ALLERGIC RHINITIS: EOSINOPHILIC OTITIS MEDIA

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Eosinophilic otitis media (EOM) is a newly recognized middle ear disease, which was first reported by Tomioka et al. in 1994. EOM is an intractable otitis media characterized by the presence of a highly viscous yellow effusion containing many eosinophils (Figure 1). It mainly occurs in patients with asthma and is resistant to conventional treatments for otitis media.

KEY MESSAGES

- Eosinophilic otitis media (EOM) is an intractable otitis media characterized by the presence of a highly viscous yellow effusion containing eosinophils. It mainly occurs in patients with asthma
- High level of eosinophil cationic protein in middle ear effusion and many EG2 immunopositive cells in the middle ear mucosa are detected in EOM patients, indicating active eosinophilic inflammation
- EOM causes deterioration of bone conduction hearing levels, particularly for high frequencies
- Systemic or topical administration of corticosteroids is the most effective treatment for patients with EOM

PATHOGENESIS

In the middle ear of patients with EOM, active eosinophilic inflammation appears to be present because high levels of eosinophil cationic protein in middle ear effusion (MEE) and many EG2 immunopositive cells in the middle ear mucosa are detected. EOM patients show a significantly longer Eustachian tube opening duration compared with that of control patients allowing antigenic materials to enter the middle ear, causing eosinophilic inflammation in association with an atopic predisposition. Antigen-specific IgEs against inhalant and bacterial antigens were detected in EOM, suggest-

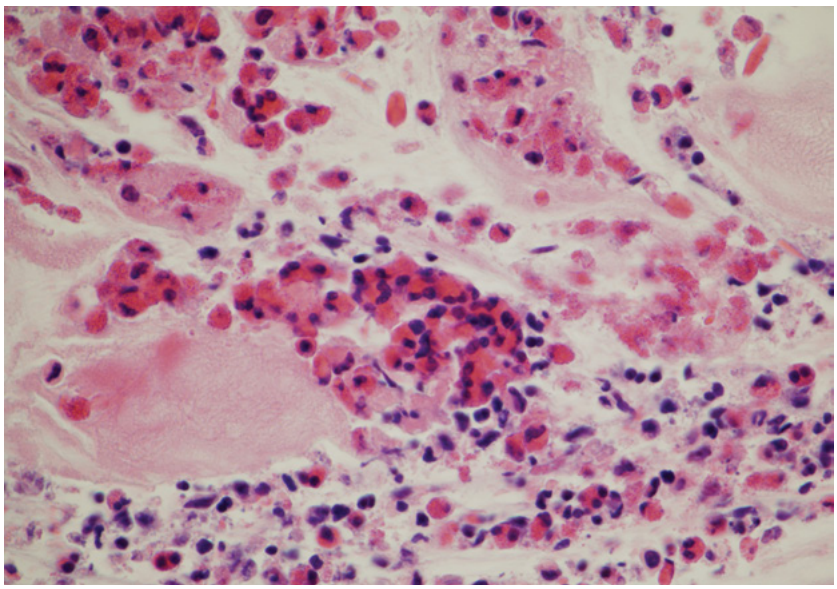

Figure 1 Histological findings of the middle ear effusion of eosinophilic otitis media. Numerous eosinophils are seen in the effusion. (HE stain)

Figure 2 Otoscopic findings of EOM, chronic otitis media type (granulation tissue formation subtype), left ear.

ing local sensitization (middle ear) against fungi and bacteria such as *Staphylococcus aureus*.

DIAGNOSIS

Diagnostic criteria were established in 2011 by the EOM study group. The major diagnostic criterion is otitis media with effusion or chronic otitis media with eosinophil-dominant effusion. The minor criteria are: 1) highly viscous MEE; 2) resistance to conventional treatment for otitis media; 3) association with asthma; and 4) association with nasal polyposis (NP). Definite cases are defined as the presence of the major criterion plus two or more of the minor criteria. In addition eosinophilic granulomatous polyangitis (Churg-Strauss syndrome) and hypereosinophilic syndrome need to be excluded.

CLINICAL FEATURES

EOM can be roughly divided into effusion type otitis media and chronic type otitis media. The latter is further divided into two subtypes: simple perforation subtype and granulation tissue formation subtype (Figure 2). About 90 % of EOM patients have asthma. Association of chronic rhinosinusitis (CRS) was also found in 75% of the patients (2). In these patients, massive infiltration of eosinophils is observed in NP or in the sinus mucosa. This condition is called eosinophil-dominant NP or eosinophilic CRS.

EOM causes deterioration of bone conduction hearing levels, particularly for high frequencies. The risk factors of deteriorating bone conduction hearing levels include high levels of IgE and eosinophil cationic protein in MEE, male sex, the duration of EOM, the severity of middle ear mucosa inflammation, and the presence of bacterial infection.

TREATMENT

Currently, the most reliable treatment for EOM is systemic and topical administration of corticosteroids. The instillation of triamcinolone acetonide into the middle ear is very effective for the control of eosinophilic inflammation.

In addition, omalizumab, a recombinant humanized monoclonal anti-IgE antibody, has been reported to be efficacious for some patients with EOM.

The control of bacterial infection is also important for the treatment for EOM superinfected with pathogens.

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3d CO-MORBIDITIES OF ALLERGIC RHINITIS: EOSINOPHILIC ESOPHAGITIS

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KEY MESSAGES

- Eosinophilic Esophagitis (EoE) is a rapidly occurring disease with symptoms of esophageal dysfunction with isolated eosinophils infiltrating the esophagus
- The diagnosis of EoE increases during pollen season
- Esophageal eosinophilia is seen in patients with allergic rhinitis and increases during pollen season to the range seen in food induced EoE
- Patients with EoE need to be treated for their allergic rhinitis

WHAT IS EOSINOPHILIC ESOPHAGITIS?

Eosinophilic Esophagitis (EoE) is a chronic immune and antigen mediated disease (Figure 1), which is characterized by eosinophil infiltration into the esophageal epithelium and results in esophageal fibrosis and dysfunction. EoE affects children and adults throughout the world, and has been reported in all continents. The prevalence of EoE is 56.7/100,000 and is increasing throughout the world. Current consensus diagnostic guidelines for EoE recommend a minimum threshold of 15 eosinophils per high power field on at least one esophageal biopsy specimen, with eosinophilia limited to the esophagus. Common macroscopic endoscopic findings include furrowing, white mucosal plaques, esophageal trachealization, esophageal narrowing, stricture, and mucosal tearing.

EoE is known to be a food antigen-driven, chronic allergic disease. There are two main currently accepted clinical treatment strategies for EoE: dietary elimination and corticosteroid treatment. Food avoidance by elemental diet or specific food elimination diet leads to resolution of his symptoms and normalization of esophageal biopsy.

Patients with EoE often have a history of atopy, such as elevated serum IgE, peripheral eosinophilia, allergic diseases (including asthma, atopic dermatitis, or allergic rhinitis, IgE mediated foods allergies), and sensitization to foods and aeroallergens as demonstrated by a positive skin test result. Allergic rhinitis (AR) was seen up to 75% of the patients.

Evidence suggests that aeroallergens may play a causative role in the development of EoE. Circumstantial evidence shows an increase in EoE diagnosis in pollen seasons. During pollen season, there is an increased numbers of eosinophils in esophagus compared to non-atopic controls, although the number of eosinophils observed was lower than values typically seen in patients who have EoE. In addition, we have seasonal variation of symptoms and eosinophils in esophagus in about 25% of our patients. Seasonal variation was confirmed in a case report on one 20 year old, full disease control was achieved only during non–pollen seasons.

Additional evidence comes from trials of allergen immunotherapy (AIT) as EoE occurred when one patient started on sublingual immunotherapy. Two recent case reports have show improvement in EoE with birch pollen and dust mites subcutaneous immunotherapy suggesting a role for aeroallergens in a select group of EoE patients.

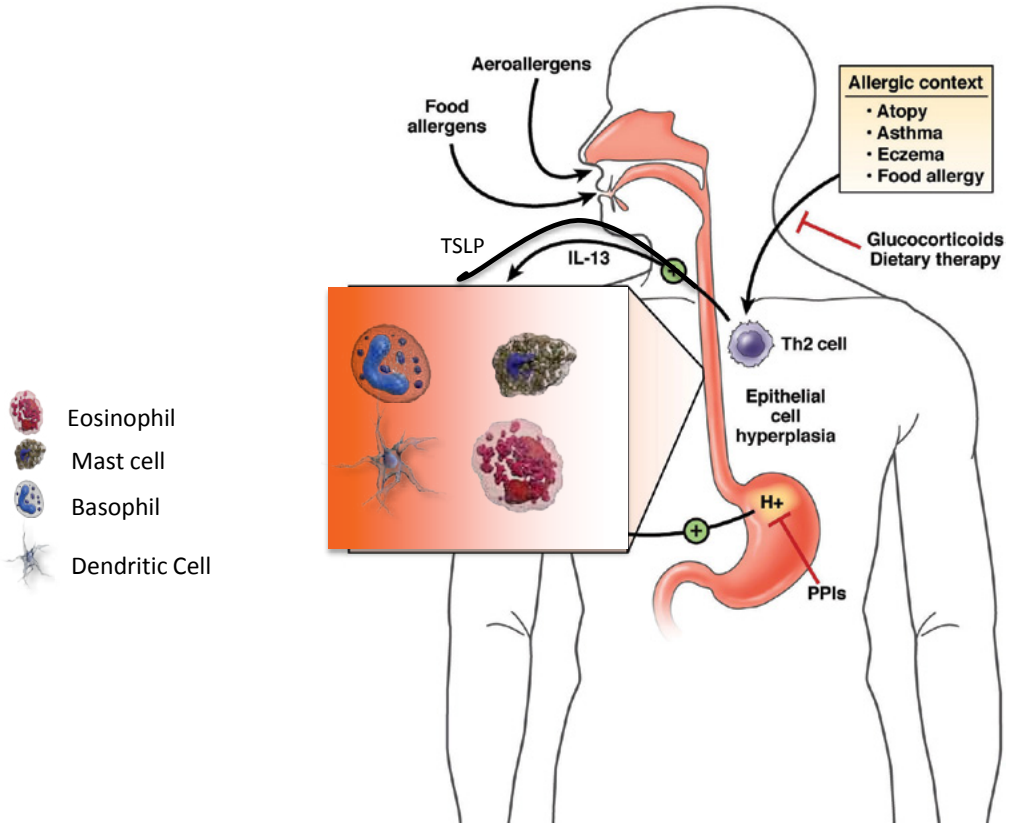

Figure 1 In genetically susceptible individuals, antigens (i.e. foods or aeroallergens) and irritants (i.e. acid reflux) induce esophageal epithelium to produce thymic stromal lymphopoietin (TSLP) and Eotaxin 3 (CCL26). Eotaxin 3 (CCL26) recruits eosinophils to the esophageal epithelium, whereas TSLP leads to dendritic cell and basophil activation as well as Th2 polarization. This results in Th2 cytokine (IL-4, IL-5 and IL-13) secretion and the development of typical Th2 inflammation characterized by eosinophils, mast cells and T cells. IL-13 further promotes expansion and survival of the recruited eosinophils. Diet therapy removes the allergen, while swallowed corticosteroids decrease pro-inflammatory cytokines. (*Figure revised from Rothenberg et al, Gastroenterol 2009 and Merves et al, Annual Allergy Asthma Immunol, 2014.*)

Nevertheless, food elimination is the mainstay of therapy for the treatment of EoE. For the seasonal induced EoE, either intranasal steroids or subcutaneous immunotherapy are available treatment options.

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4 THE UNITED AIRWAY DISEASE

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KEY MESSAGES

- The respiratory tract starts with the nose and ends with the peripheral small airways
- Nervous triggers and inflammatory changes in the upper airways relate to changes in the lower airways, mediated through a nervous, direct and systemic route
- Optimal control of asthma involves proper treatment of the associated rhinitis or rhinosinusitis

The airways start with the nose and end with the peripheral small airways. Thus the nose has an important role as gatekeeper protecting the lower airways from exogenous pro-inflammatory triggers. The nose and bronchi form one respiratory unit (Figure 1).

Anatomically there are both similarities and differences. The nose is being formed by the ectoderm, while the lower airways derive from the mesoderm, with the paranasal sinuses representing a mix of these two. Thus the nose keep some features from the skin being more resistant to external stress compared to mucosa of the lower airways. One common feature of the facial skin and the nose and the lung is the innervation.

THE NERVOUS LINK

Both the face and the nose are sensitive to external stimuli potentially harmful for the lower airways. Koskela described in a study on cold air sensitive asthmatics that facial cooling was enough to induce a bronchial obstruction in subjects inhaling humidified room tempered air. The magnitude of response was the same as when the subjects inhaled cool dry air to the lower airways.. However, not only the face but also the nose share the same pattern with efferent sensory nerves mediating a response in the lower airways. In a study by Millqvist, cold air stimuli in the nose induced increased resistance of the lower airways. This naso-bronchial reflex could be suppressed by local anesthesia applied in the nose. A third evidence of a nervous link between the upper and lower airways was the study by LIttell showing that methacholine but not histamine applied in the nose, increased both nasal and lower airway resistance.

THE DIRECT AIRWAY LINK

During inspiration the air is filtered, tempered, humidified and supplied with nitric oxide (NO) before entering the lower airways. Thus the nose serve as an important conditioner of the air that is tracked down into the airways. Nose breathing can prevent bronchoconstriction induced by inhalation of cold dry air, and increased mouth breathing due to a blocked nose is likely to be one reason for the worsening of asthma. In normal controls almost all NO found in exhaled air is derived from the upper airways, mainly produced in the paranasal sinuses. During deep nasal inhalation, NO in physiological concentrations is being tracked down to the lower airways. This is believed to be an important factor that helps to improve matching between ventilation and perfusion.

A SYSTEMIC LINK

Allergen challenge in the nose is know to induce inflammatory changes in the bronchi, measured as increased numbers of eosinophils in bronchial mucosa. The final proof that the reaction was due to

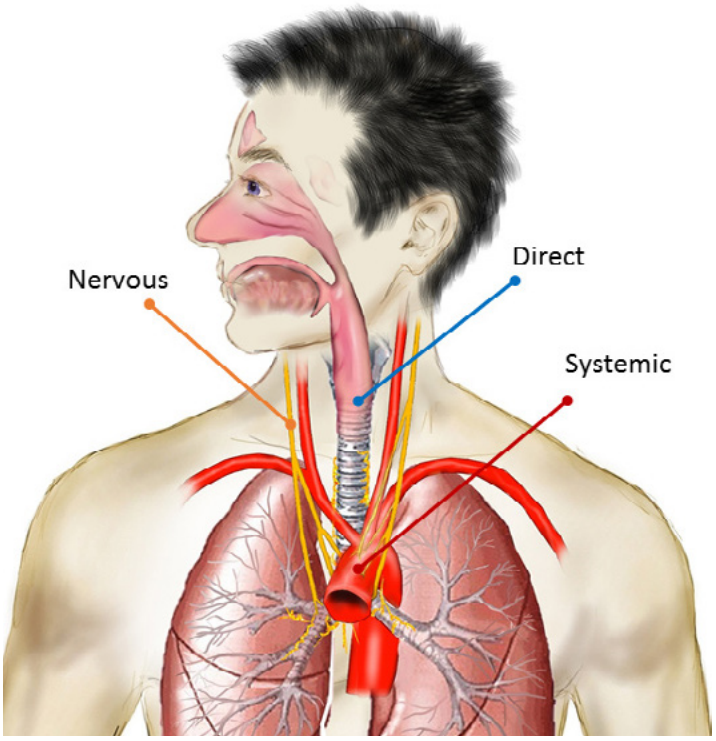

Figure 2 There is a consistent link between the nose and the lower airways, forming one functional unit. A direct link, a systemic link and a nervous link have been documented.

systemic mechanisms came from the revert study applying allergens by endoscopy in the lower airways, and than 24 hours later, showing increased inflammation in the nasal mucosa. The link between the paranasal sinuses and the lower airways is probably even more interesting. Sharing the same germ layer origin, there are similarities not only regarding cellular inflammation but also in tissue inflammation and remodelling. A chronic sinusitis harboring fungal or staphylococcal superantigens has been associated with a more extensive and difficult to treat asthma. Also in other non-asthmatic conditions, a definite link exist, i.e. chronic lower airway infection with bronchiectasis is associated with an increased prevalence of chronic sinusitis with polyps.

IMPLICATION FOR TREATMENT

The link between the upper and the lower airways is so obvious that it should be regarded as misconduct not to consider both compartments as treatment targets in order to achieve optimal disease control. Thus patients with asthma and more severe rhinitis or rhinosinusitis have a greater risk of worsening asthma control and getting severe asthma exacerbations. In parallel, severe asthma barely exists without concomitant rhinosinusitis. In the traditional asthma studies, severe rhinitis patients have been excluded. Therefore, we need to explore different treatment alternatives, how to best treat and control asthma and rhinitis simultaneously. This can be done either as optimal local treatment by the two compartments or by the systemic route. As new biologics with anti-cytokine treatment are entering the scene, it is important that these aspects are being addressed from the early start.

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5 ATOPIC DERMATITIS AND ALLERGIC RHINITIS: WHERE IS THE EVIDENCE FOR COMORBIDITY?

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KEY MESSAGES

- There is clear evidence for comorbidity between atopic dermatitis (AD) and allergic rhinitis (AR)
- AD usually precedes AR and the association strongly depends on the stage of the course of AD
- Future early prevention strategies may decrease the incidence of both AD and AR

Atopic dermatitis (1), allergic rhinitis (AR) and allergic asthma (AA) (2) represent the three allergic diseases within the context of the atopic diathesis. Interestingly, while the issue of comorbidity between AD and AA has been analyzed thoroughly from a genetic, epidemiological and clinical aspect, data related to the comorbidity between AD and AR are more scarce. In principle, this could be mainly due to the fact that the age of onset of both diseases differs substantially. Indeed in our classical view, AD starts rather early in childhood and typically much longer before AR and AA emerge. However, epidemiological studies seem to show that the combination of AD and AR is a risk factor for AA. Moreover, the issue of the severity of AD and its possible implication for the appearance of AR has not been studied in detail.

In some epidemiological studies looking at the prevalence of AD, AA and AR, the percentage of subjects with both AD and AR was about 9%. Interestingly, this prevalence of comorbidity decreased afterwards with age. The BAMSE cohort reported a higher incidence: at 12 years, 58% of the children had eczema, asthma and/or rhinitis (Figure 1) at some time. Disease turnover was high for all three diseases throughout the study (Figure 2). Comorbidity increased with age, and at 12 years, 7.5% of all the children were affected by at least two allergy-related diseases. This further illustrates how important it is to consider the age of the patients and disease turnover with regard to this particular kind of association. It is well accepted that patients with AD are significantly more likely to have other atopic diseases, compared to patients without AD (22% versus 17%). In such studies, which are not primarily considering the age of the patients, the comorbidity between AD and AR was quite high (76 %). In other studies a higher percentage of patients with AD had reported to have rhinitis but again these studies did not consider differences in terms of age of the patients. Interestingly from a genetic point of view, there is no evidence for a clear overlap in terms of genetic linkage analyses or by the means of other genetic investigations such as genome wide association studies.

Moreover there are no clear-cut validated biomarkers identified so far which may predict, that a given patients with AD will develop AR in the course of the natural history of its skin disease. On the other hand, it has been reported that individuals with AD clearly show a predisposition for allergic comorbidities by the age of 3y and that this seems to correlate with the severity and poor disease control of AD.

This is again confirmed by more recent studies looking at the severity of AD in relationship with other

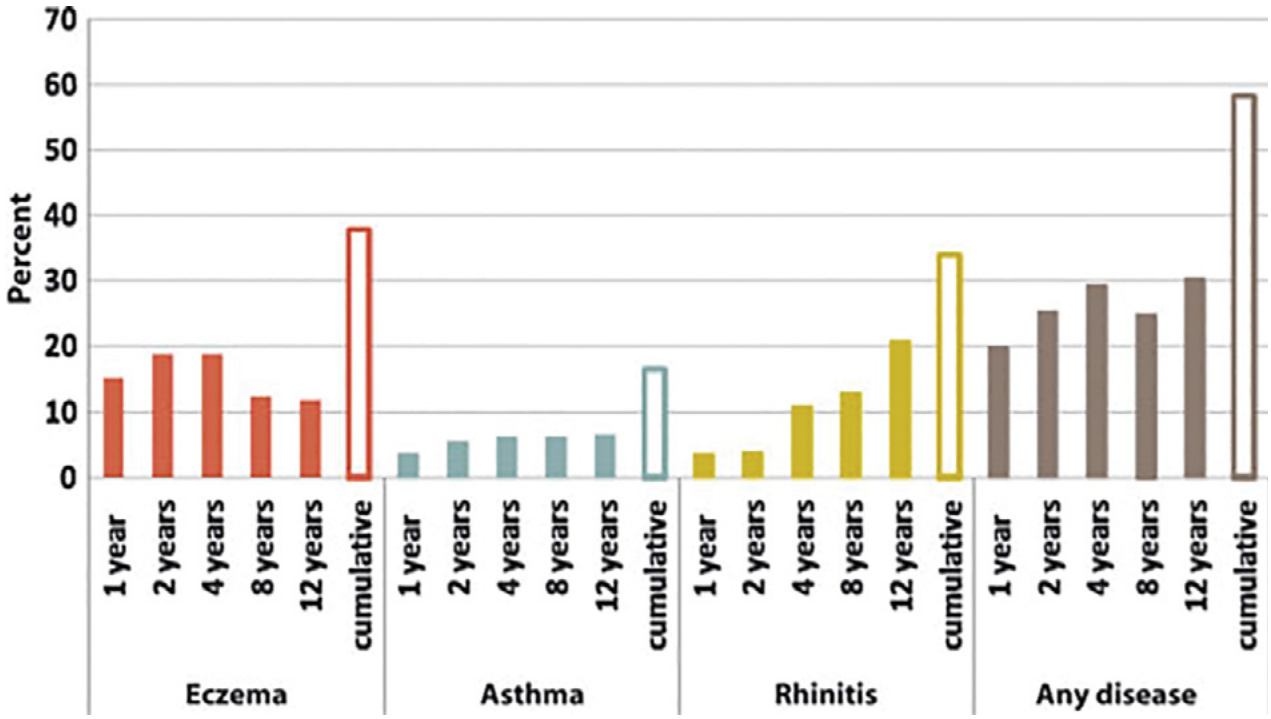

Figure 1 Prevalence rates of allergy-related diseases up to 12 years in the BAMSE birth cohort. Twelve-month prevalence of eczema, asthma, rhinitis and any symptom at age 1, 2, 4, 8 and 12 years. Empty bars show the cumulative prevalence at 12 years (n=2916). (*Reproduced with permission from Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. Allergy, 2012;67:537-544, with permission from Willey Blackwell.*)

chronic health disorders including AA, AR and food allergies. Hence addressing the question of comorbidity of AD and AR seems to be tightly related to the time point at which the patients are observed during the course of AD. Indeed, beside the real comorbidity, sequential association between AD and AR is probably the more often situation than the single occurrence of both allergic diseases.

The lessons learned from these observations as 3 fold:

1. The heterogeneity of the clinical phenotype of AD has so far been underestimated. New epidemiological studies with regard to the question of the comorbidity should consider this particular aspect.
2. In terms of prevention, there are currently new developments aimed to prevent the appearance of AD as the first manifestation of the atopic march by a very early intervention using emollients directly after birth. Only a few studies have addressed this key issue so far and it will be interesting to see whether a successful prevention of AD in the context of this early intervention may also prevent the appearance of AR in children with high risk to develop the atopic march.
3. From a therapeutic point of view it is well accepted that - in contrast to AR -antihistamines have only poor effects in the control of AD, particularly with regards to the pruritus. On the other hand, there is some evidence that allergen immunotherapy (AIT) targeting for example house dust mite as a classical trigger for AR could be of interest in the context of the management of the severe forms of AD. Clearly, for such studies we needed to explore the clinical benefit but also the immunological mechanisms putatively involved in a positive clinical respond for both AD and AR to AIT.

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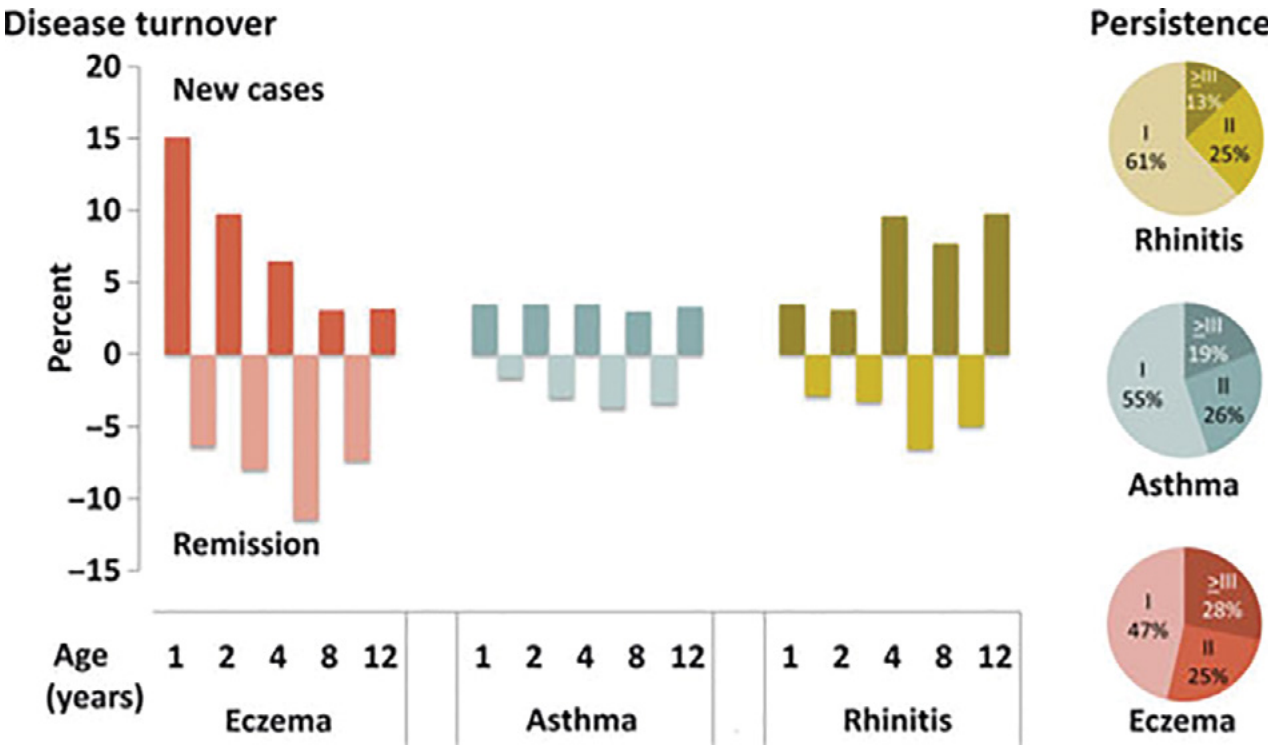

Figure 2 Disease turnover and persistence up to 12 years of age in the BAMSE birth cohort. Turnover indicates the percentage in the population (n = 2916) of new and remitting cases at each observation point. New cases were defined as onset of disease that had not been present at any previous observation point, and remission was defined as not having a disease that had been present at the previous observation point. Persistence indicates the proportion of children who had a disease at one, two, three or more observation points among the children who had ever had the same disease. (*Reproduced with permission from Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. Allergy, 2012;67:537-544, with permission from Willey Blackwell.*)

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6 ALLERGIC RHINITIS AND FOOD ALLERGY

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Food allergy is an overlooked co-morbidity of allergic rhinitis (AR), however the upper respiratory tract can be a target of IgE-mediated food allergy. Symptoms may include nasal congestion, rhinorrhoea, sneezing and pruritus. Although prevalence seems to be low in clinical presentation, patients who present with IgE-mediated food allergy have nasal symptoms during oral food challenges.

A peculiar form of co-morbid food allergy, highly prevalent in patients with pollen-induced AR, is the so called "pollen food syndrome" (PFS), which is also termed "oral allergy syndrome" (OAS). This is an immediate hypersensitivity reaction mediated by IgE following sensitization to pollens. Patients will experience local oral symptoms of pruritus and swelling with fresh fruits (e.g. apple, pear, peach), vegetables or spices that cross-react with pollens (Figure 1 and Table 1). The suggested mechanism is IgE cross-reactivity between the implicated plant-derived food and the primary sensitizing pollen(s) that occurs as consequence of common epitopes between pollen and food allergens.

The pathogen-related proteins (PR) are the plant allergens responsible for this peculiar form of food allergy. Some of them are heat–resistant and account for some more severe reactions. Two main families of heat-labile PR have been identified as more prevalent in inducing clinical reactions: the Bet v 1 family (birch pollen major allergens that are highly cross reactive with several plant food allergens) and the profilins (which includes the Bet v 2 minor

KEY MESSAGES

- Adolescents and adults suffering from allergic rhinitis (AR) can develop oral symptoms to raw fruits and vegetables. This syndrome is called pollen–food syndrome or oral allergy syndrome. It is characterized by an IgE-mediated, immediate reaction induced by prior sensitization to pollen rather than primary sensitization to a food allergen. Cross-reactivity depends on specific epitopes shared by food allergens and pollen
- Pathogenesis-related proteins (PR) are usually responsible for these reactions. 17 families of PR have been identified according to their function. The most relevant to pollen food allergy syndrome are profilins (PR-10), lipid–transfer–protein (LT; PR-14 and PR-15)
- Profilins in birch pollen cross –reacts commonly with foods of the Rosacee family i.e for fruit: apple, pear, peach, cherry, apricot. Bet v 1 shows homologous protein with Mal d 1, a major antigenic protein in apple
- The clinical manifestations are usually mild and transient (pruritus of the lip, tongue and mouth, throat tightness). Systemic reactions are uncommon, but may happen depending on the specific epitope that is involved
- Symptoms are triggered by fresh vegetables and fruits. The cooked forms are usually tolerated
- The prevalence is related to sensitivity patterns varying with exposure and is associated to geographical areas i.e Northern Europe: birch pollen/apple, Southern Europe: grass pollen/apricot, pear, apple

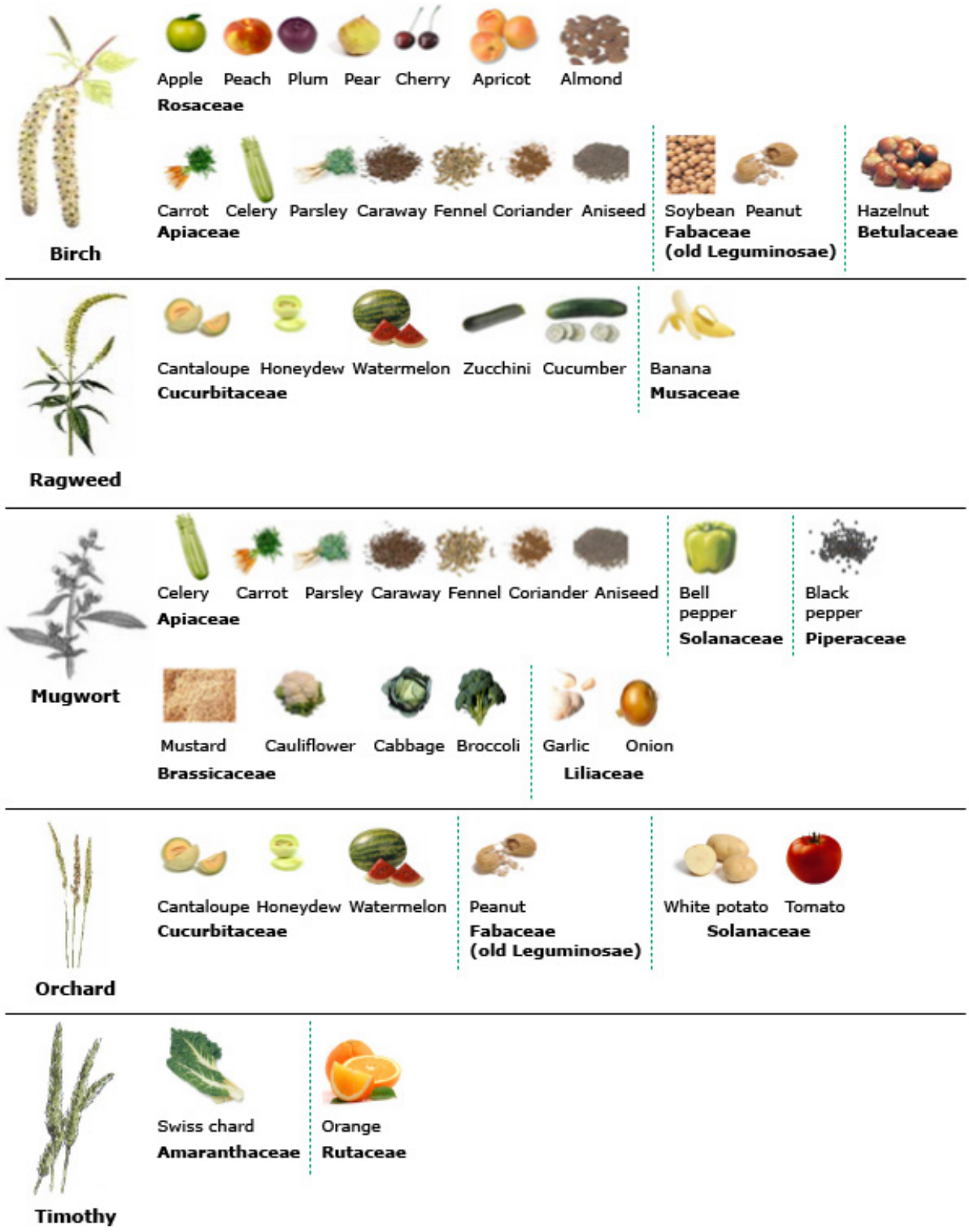

Figure 1 Cross-reactive pollens and foods

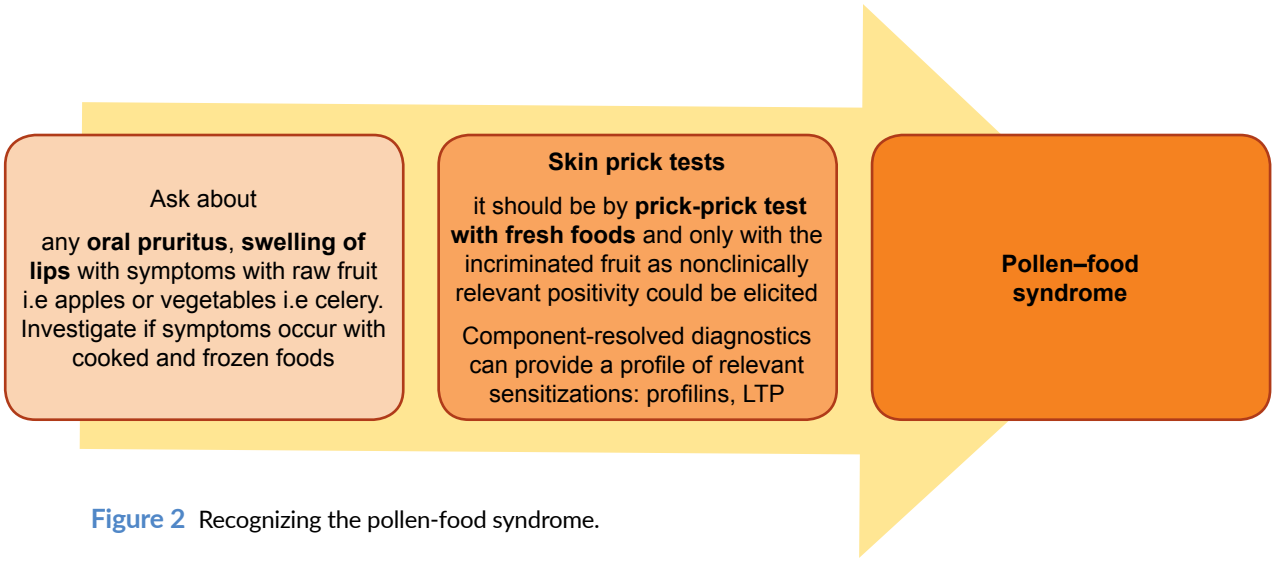

Figure 2 Recognizing the pollen-food syndrome.

TABLE 1

Cross-reactive pollens and foods	
Birch	Apple, pear, cherry, peach, nectarine, apricot, tomato, kiwi, carrots, potato, parsnip, green pepper, fresh spices, celery, peanuts, hazelnut, walnut, almond, lentil, beans, peas, soybean
Grass	Melon, water melon, oranges, tomato, potato, kiwi, Peanut, carrot
Mugwort	Celery, carrot, spices (parsley, caraway seeds, fennel seed, coriander seeds, aniseed, paprika, garlic, onion) pepper, mango, leek, mustard, broccoli, cabbage, cauliflower, chamomile, kiwi
Ragweed	Melon, Zucchini, Cucumber, Banana
Pellitory	Pistachio, Swiss chard
Olive	Pollen Peach, pear, melon, kiwi

birch pollen allergen, also highly cross reactive with other pollen and plant derived food allergens).

The prevalence and pattern of the triggering food can vary widely in relation to the specific regional pattern of sensitization. Oral symptoms related to birch pollen are more prevalent in Northern and Central Europe, while in Southern Europe grass pollen is the usual trigger.

Diagnosis (Figure 2) relies on a history of pruritus at the lip and tongue, sometimes with oral and facial angioedema and throat tightness following the ingestion of fruit and vegetable. Skin prick testing with the raw fruit and vegetable is more accountable than using commercial extract, as the allergens are usually labile and are easily destroyed by cooking. The use of component–resolved–diagnostics has recently allowed to better profile the sensitizations of these patients and to add some probabilistic information on the severity of the reactions. The only treatment is avoidance of the triggering food; the role of inhalant allergen immunotherapy as treatment of the clinical reactions to related foods is still debated. Prevention of PFS avoiding all the possible cross-reactive foods in pollen allergic patients has not be shown to be effective.

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7 THE LINK BETWEEN THE SKIN AND THE AIRWAYS

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KEY MESSAGES

- Non-specific mast cell mediator symptoms, including fatigue, arthralgia and hyperacidity may be experienced by patients with severe chronic urticaria, but symptoms in the respiratory tract resulting from local mast cell degranulation are not usually described
- By contrast, involvement of the respiratory tract in allergen-induced anaphylaxis with urticarial rash is well known
- There is limited evidence for bronchial hyperreactivity and subclinical asthma in patients with spontaneous and inducible types of chronic urticaria. Studies are required to look for evidence of subclinical rhinitis in severely affected chronic urticaria patients

The cutaneous mast cell is considered to be the primary effector cell in urticaria and histamine to be the major mediator, although there is clinical and histological evidence that other inflammatory events are important. Histamine is also considered to be a key mediator of allergic rhinitis (AR). Unlike chronic urticaria (CU), where IgE-mediated allergy is rarely the cause, a high proportion of AR patients are allergic to inhalant allergens and will develop symptoms on exposure.

It might be anticipated that CU patients would have features of generalized mast cell degranulation if the autoimmune hypothesis of causation is correct. Although patients with severe urticaria may complain of non-specific fatigue, arthralgia and indigestion due to mediator release into the circulation, it is exceptional for patients to experience respiratory or gastrointestinal symptoms during attacks. A possible explanation for this is the need for co-stimulation of cutaneous mast cells by C5a at the time of activation by functional autoantibodes against IgE or its receptor. By contrast, resident mast cells of the respiratory tract do not express the C5a receptor and therefore do not respond to direct or indirect cross-linking of the high affinity IgE receptor by autoantibodies. This is in contrast to acute urticaria, which may be caused by immediate hypersensitivity reactions to food or drug allergens with a risk of progression to anaphylaxis. Symptoms result from generalized mast cell degranulation, including local release of histamine and other mediators in the respiratory tract leading to rhinitis and/or asthma.

There is some evidence for bronchial hyperreactivity in different subtypes of CU although overt asthma is rare. One study concluded that bronchial hyperresponsiveness is a common feature in patients with active CU. Twenty six adults with chronic spontaneous urticaria were assessed with respiratory function tests and methacholine provocation. Two had asthma on baseline pulmonary function tests and twenty others (77%) showed bronchial hyperresponsiveness on methacholine challenge. Bronchial hyperresponsiveness has also been demonstrated in patients with cholinergic urticaria and symptomatic dermographism. A retrospective questionnaire sent to parents of children presenting to a paediatric allergy centre identified respiratory symptoms during

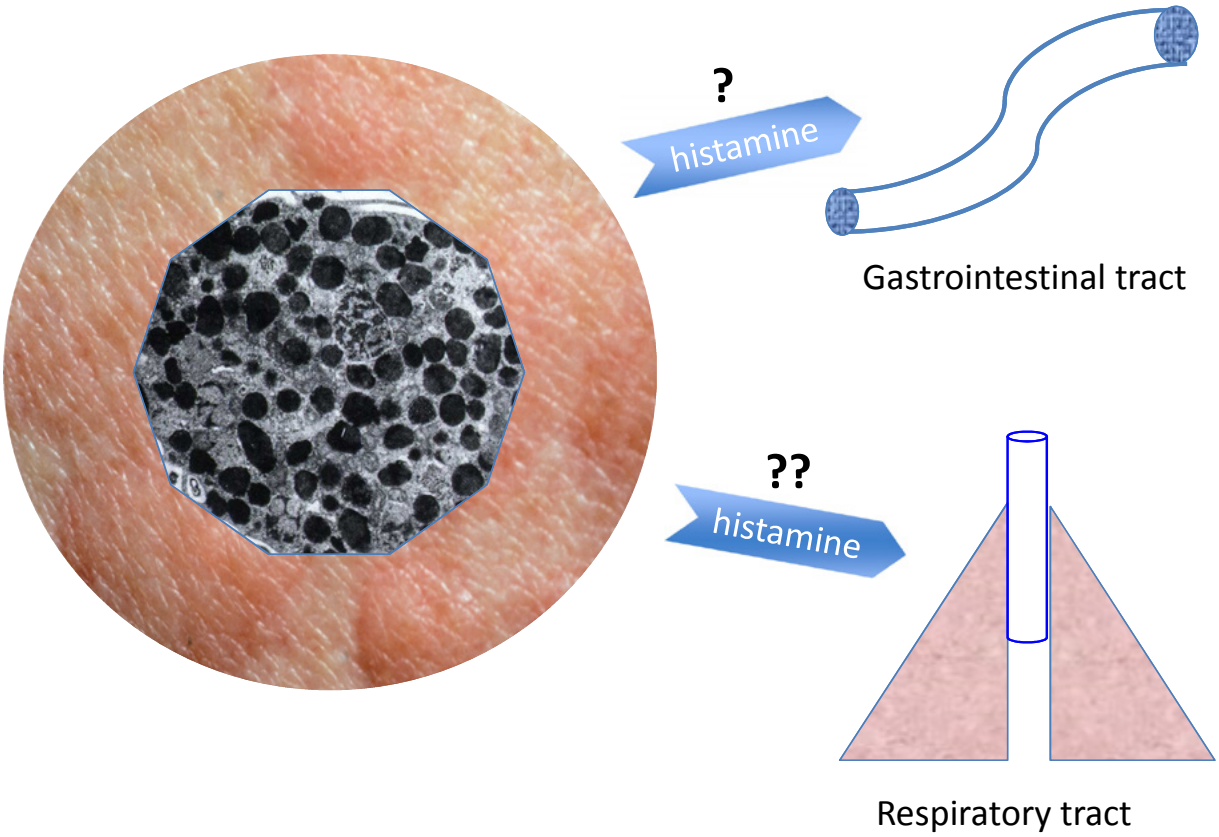

Figure 1 Urticaria results from mast cell mediator release in the skin. Systemic features in severe chronic urticaria may include hyperacidity in the gut and bronchial hyper-responsiveness of the airways. These may result from distant effects of circulating mediators from cutaneous mast cell degranulation, including histamine, rather than local tissue degranulation in gut and lung.

attacks in 6/45 children (13%) although the authors did not detail whether they related to the upper or lower respiratory tract. It seems possible therefore that evidence for subclinical upper respiratory tract involvement in severe chronic urticaria may be found with appropriate studies.

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8 ALLERGIC RHINITIS AND ANGIOEDEMA

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KEY MESSAGES

- Angioedema is a severe and potentially life- threatening condition
- Angioedema with urticaria is common, mostly histamine-induced and responds to systemic antihistamines and steroids
- Bradykinin-mediated forms are rare and mosty induced by hereditary or acquired deficiency in C1-Inhibitor (function) or by drugs, namely ACE inhibitors. Treatment of acute attacks is based on C-1 Inhibitors or bradykinin receptor antagonist
- Little is known about mutual between allergic rhinitis and angioedema; worsening by cumulative effects may occur

Angioedema is often a severe and potentially life- threatening condition with substantial impact on the patients' quality of life. Severe symptoms such as laryngeal blockage but also disabling swellings or strong abdominal pain due to intestinal angioedema require immediate, specific and fast acting therapy. Thus every physician caring for patients with diseases in the oro-pharyngeal area should be familiar with a basic knowledge on the management of angioedema. There are 2 different forms of angioedema based on different mediators and partly also clinical features: Histamine- mediated forms and non-histamine, bradykinin-mediated diseases (Figure 1).

HISTAMINE-AND OTHER MAST CELL MEDIATOR MEDIATED FORMS OF ANGIOEDEMA

Histamine-mediated forms are mostly associated with urticarial, itch and/or systemic allergic symptoms such as asthma or anaphylactic shock; untreated they lasts often mostly for a few hours before spontaneously resolving. Acute forms are often para-infectious or due to immediate allergic reactions to causes such as drugs (aspirin, NSAIDS and others), hymenoptera venom (honey bees, wasps) or foods. Accordingly to the severity treatment is based on antihistamines (H1-blockers), steroids and in severe cases intramuscular adrenaline. Chronic forms with a duration of more than 6 weeks are often so-called spontaneously with no definite underlying cause. Treatment is similar as in chronic spontaneous urticaria involving updosing 2nd or 3rd generation antihistamines (H1- blockers) and in non-responding cases increasingly also Omalizumab.

BRADYKININ-MEDIATED FORMS OF ANGIOEDEMA

Bradykinin-mediated angioedema are characterized by recurrent episodes of non-pruritic subcutaneous or submucosal edema with no associated wheals and urticarial and involving extremities, bowel or facial-oropharyngeal-laryngeal region. Hereditary angioedema (HAE) due to C1 esterase inhibitor (C1-INH) deficiency and HAE with normal C1-INH and acquired C1-INH deficiency are all rare but important diseases with significant morbidity and also mortality. The swelling is induced often by minor trauma or stress and may worsen slowly but often last several days. HAE has to be separated from drug-induced angioedema: frequently by Angiotensin-Converting-Enzyme-Inhibitors (ACE—Inhibitors), but also by some glyptins, thrombolytic and immunosuppressive agents ; drug-in-

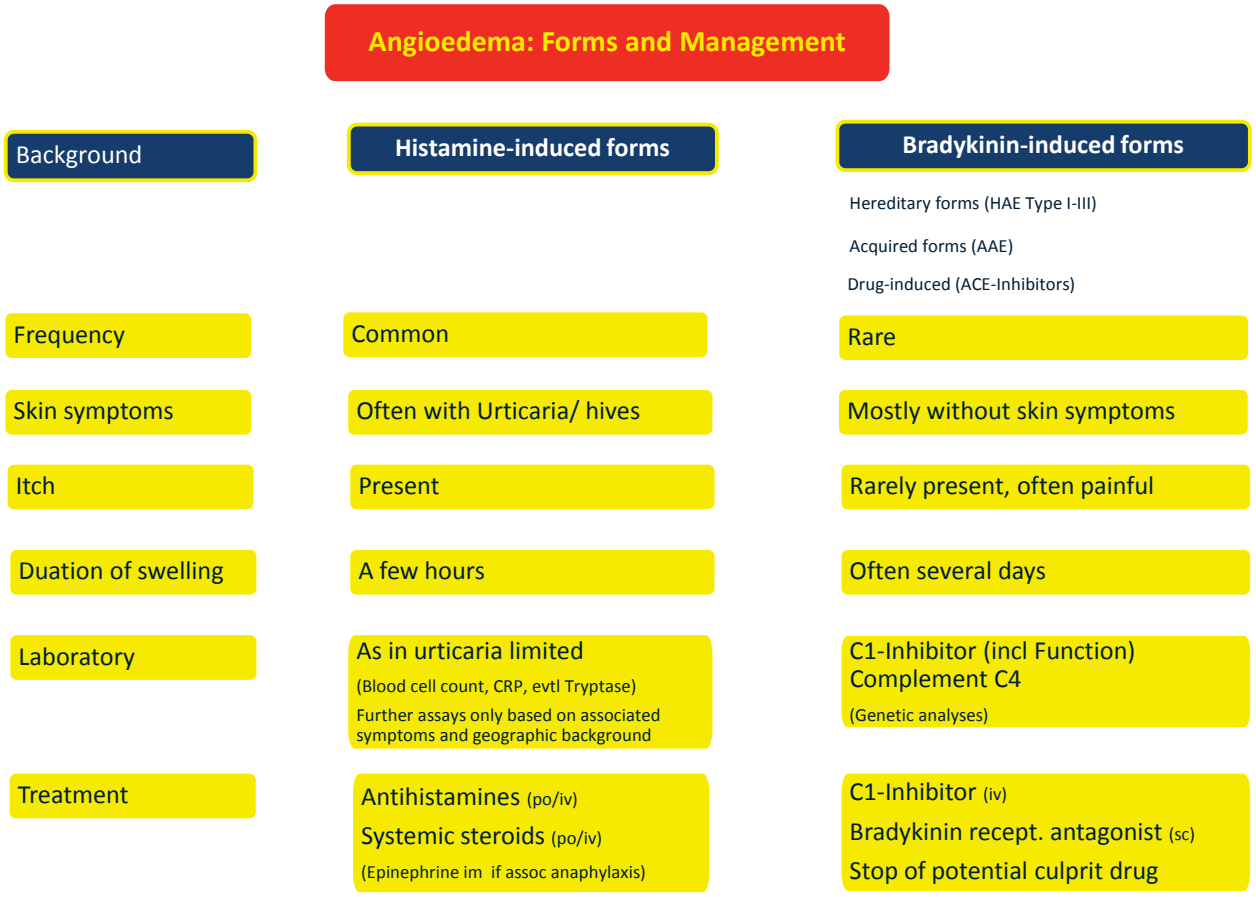

Figure 1 Distinct forms of angioedema due to different pathophysiologic background. (*Adapted from Maurer M, Magerl M, Metz M, et al. Practical algorithm for diagnosing patients with recurrent wheals or angioedema. Allergy 2013;68:816-819.*)

duced forms preferentially involve the facial-oropharyngeal region.

Diagnosis is based on clinical history and complement analyses (C1-INH value and function, Complement C4, genetics). Treatment of the acute attacks include plasma-derived C1-INH concentrates, recombinant human C1-INH and a bradykinin receptor antagonist. All are highly efficient and fast working. Typically systemic antihistamines and steroids do not work in bradykinin-mediated angioedema.

ALLERGIC RHINITIS AND ANGIOEDEMA AS MUTUALLY EXACERBATING FACTORS

Mainly acute histamine-mediated forms of angioedema in patients with allergic rhinitis e.g. with associated food allergy can lead to severe comorbidity and cumulative worsening of both diseases. Little is known about allergies as an exacerbating factor of bradykinin-mediated angioedema; however recently a certain exacerbation of ACE-I induced angioedema during pollen season has been reported.

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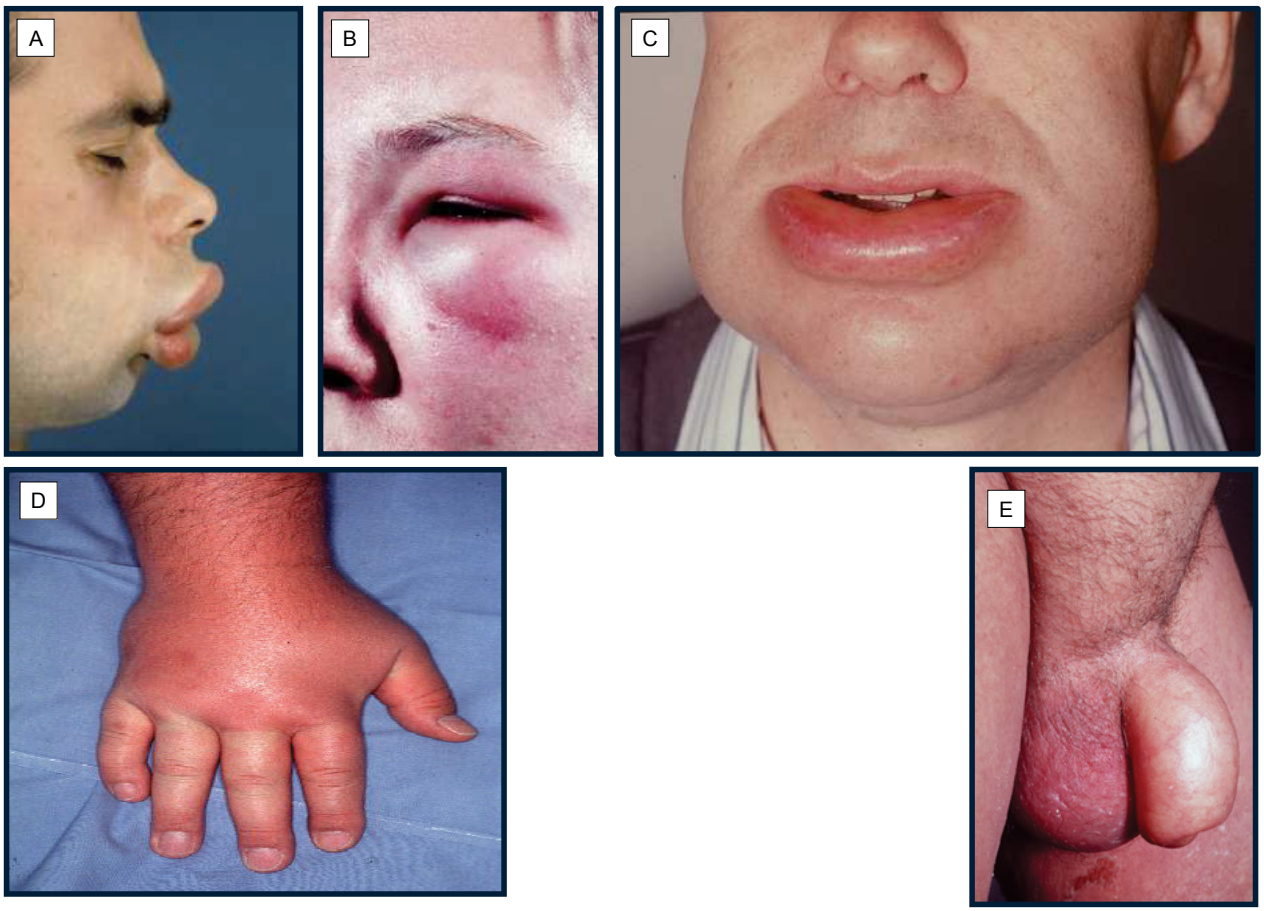

Figure 2 Different manifestations of angioedema with facial involvement (A-C), hand (D) and genitalia (E) due to NSAID hypersensitivity (A), ACE Inhibitor induced (B) and HAE with C1-Inh deficiency (C, D, E)

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9 ALLERGIC RHINITIS AND SLEEP APNEA

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KEY MESSAGES

- Allergic rhinitis can contribute to worsening of obstructive sleep apnea syndrome (OSAS) due to elevated inspiratory breathing workload
- Nocturnal allergic rhinitis and asthma can mimic symptoms of OSAS
- Patients with OSAS present with nocturnal snoring, choking, and stops of breathing. In addition, they suffer from chronic excessive sleepiness and nonrestorative sleep
- OSAS is diagnosed by polysomnography; a cardiorespiratory polygraphy can render first information about nocturnal breathing in patients suspected to suffer from OSAS
- Positive airway pressure therapy applied by a nasal mask is standard-therapy in OSAS, thus nasal breathing needs to be optimized

INTRODUCTION

Nasal obstruction results in pathologic changes in airflow velocity and resistance and has been associated with obstructive sleep apnea syndrome (OSAS) as a potential etiologic factor by promoting more negative intraluminal pressure in the pharynx predisposing to pharyngeal occlusion and thus obstructive apnea events. Although clinical research examining the correlation between nasal obstruction and sleep-disordered breathing is limited, studies evaluating patients with either naturally occuring partial nasal obstruction (e.g. allergic rhinitis, septal deviation) or experimentally induced nasal occlusion show a clear relationship between nasal obstruction and nocturnal appearance of snoring, hypopneas, and apneas. In a population-based sample (n=4927), participants who often or almost always experienced nighttime symptoms of rhinitis were significantly more likely to report habitual snoring, chronic excessive sleepiness, or nonrestorative sleep than those who rarely or never had symptoms.

NASAL RESISTANCE AND SLEEP APNEA

Rhinitis is a risk factor for sleep-disordered breathing on the basis of the Bernoulli principle (stating that the wider the beginning of a duct is, the less the risk of collapse is and viceversa) and the Venturi effect (postulating that air must pass through a small tube faster than through a large tube if the passing volume of air and time remain constant). From this perspective upper airways behave like a Starling resistor: the obstruction at the inlet induces collapsing forces that manifest downstream in the collapsible segment, the pharynx.

SLEEP APNEA AS A DIFFERENTIAL DIAGNOSIS TO NOCTURNAL ALLERGIC RHINITIS AND ASTHMA

Allergic rhinitis and allergic asthma often show a worsening of symptoms during sleep, especially when a house dust mite sensitization is present. This leads to a poor sleep quality and daytime somnolence. In contrast to these symptoms, patients with OSAS present with habitual snoring, choking and stops of breathing (apneas) during sleep. In addition, patients with

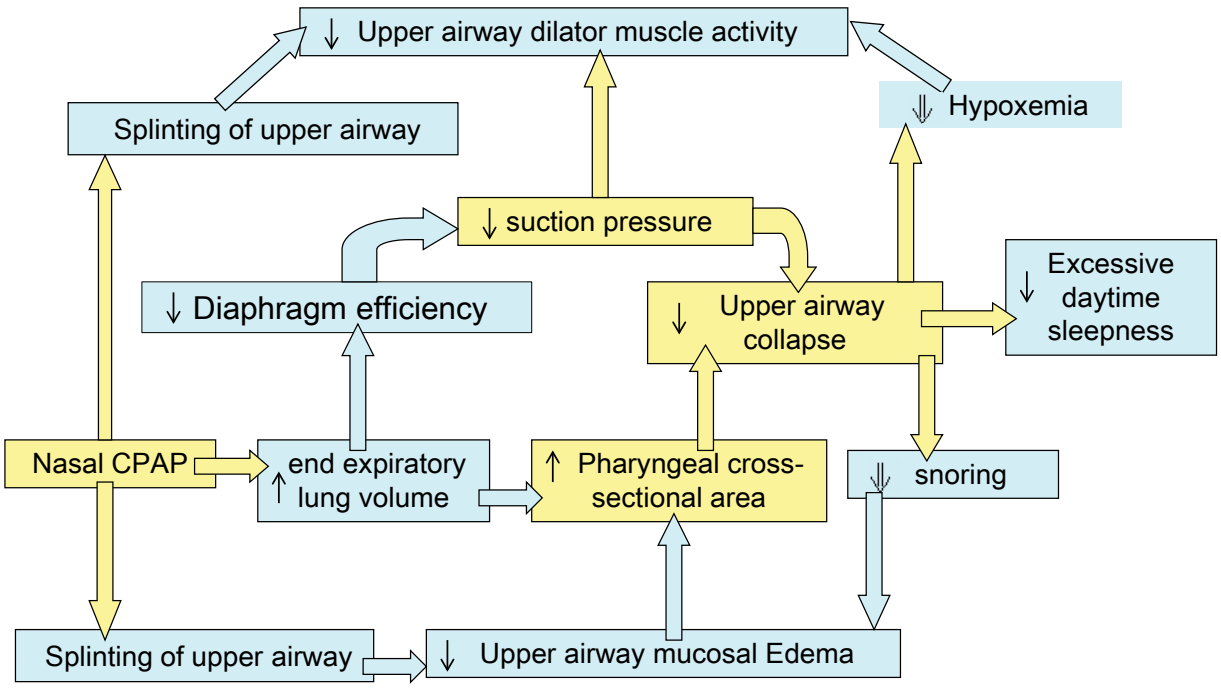

Figure 1 Potential physiological effect of nasal CPAP in patients with OSAS. (*From Breathing Disorders in Sleep Mc Nicholas WT and Philipson Saunders Elsevier Science Limited 2002 pag.118*)

OSAS suffer from chronic excessive sleepiness and nonrestorative sleep. In most cases, talking with the patient`s partner can help differentiating the underlying diseases. OSAS can effectively be diagnosed by polysomnography in a sleep lab. A non-laboratory monitoring of sleep by cardiorespiratory polygraphy can render first information about nocturnal breathing in patients suspected to suffer from OSAS.

NASAL RESISTANCE AND CPAP THERAPY

CPAP (Figure 1) is, the most effective treatment for OSAS. with a compliance rate for CPAP of approximately 60%. Nasal congestion, irritation or runny nose can be caused by the use of CPAP but, when concomitant rhinitis is present, its symptoms may intereferes with CPAP adherence. Symptoms can be often alleviated by the use of a humidifier but a proper treatment of concomitant allergies, chronic sinus problems or a deviated septum must be considered.

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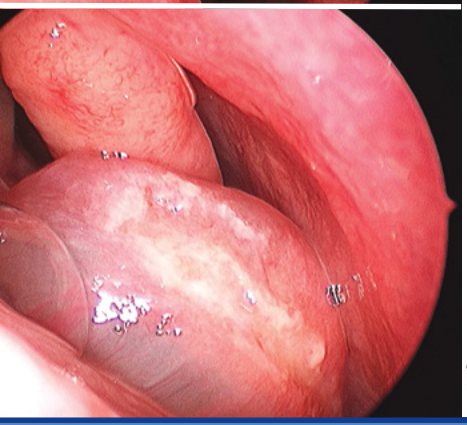
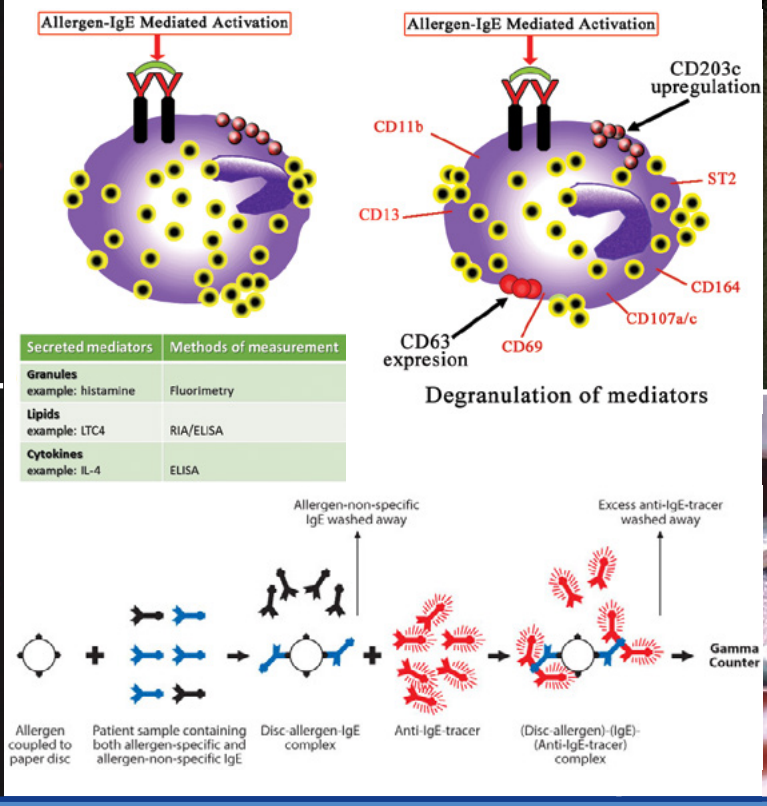
Section D





ALLERGIC RHINITIS - DIAGNOSIS

* Allergic rhinitis diagnostic work-up overview
* Diagnosis of allergic rhinitis - rhinoscopy and endoscopy
* Non-invasive evaluation of nasal inflammation (NO, nasal cytology and mediators)
* Skin testing in the diagnostic workup of rhinitis
* Provocation tests
* Specific IgE and diagnosis of allergic rhinitis
* Component resolved diagnosis
* Diagnosis of allergic rhinitis - cellular tests
* New diagnostic and research techniques in allergic rhinitis and chronic rhinosinusitis
* Measuring allergen exposure
* Diagnosis of allergic rhinitis-measuring health-related quality of life
* Biotechnology for the diagnosis of allergic rhinitis

1 ALLERGIC RHINITIS DIAGNOSTIC WORK-UP OVERVIEW

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KEY MESSAGES

- A detailed history is useful in helping distinguish between allergic rhinitis from different types of non-allergic rhinitis, but allergy testing is needed to make a reliable diagnosis, particularly when year round nasal symptoms are present
- Demonstration of sensitisation by testing is not sufficient alone to make the diagnosis of allergic rhinitis and must be correlated with clinical history
- Differential considerations for allergic rhinitis include various types of non-allergic rhinitis, rhinosinusitis and anatomic problems

To correctly diagnose allergic and non-allergic rhinitis, rhinosinusitis and other conditions that may affect the nose and sinuses, history, physical exam and when appropriate, testing should be performed.

Some symptoms of allergic rhinitis (nasal drainage, nasal congestion, sneezing, and nasal itching) overlap with some symptoms associated with non-allergic rhinitis, rhinosinusitis, (Table 1) or with other disorders that may involve the nose and sinuses. (Table 2).

By history, allergic rhinitis (AR) is more likely than non-allergic rhinitis if there are nasal itching and sneezing, associated eye symptoms (itchy, watery eyes), and nasal symptoms that develop or worsen with exposure to furry pets or seasonally in association with regional allergy pollen seasons (Table 1). Year round symptoms make it more difficult to distinguish AR from non-AR, or even chronic rhinosinusitis, on the basis of history alone. Allergy testing then is needed for a correct diagnosis. However, the mere presence of sensitisation as identified by skin testing or blood testing is not sufficient and must be correlated with the clinical history. Unilateral nasal symptoms suggest that an anatomic issue is present (Table 2).

Physical examination of the nose should be performed, in part to identify complicating or alternative nasal conditions (e.g, nasal polyps, septal deviation). In AR, inflamed mucosa classically has a bluish/ pale hue, but appearance may vary and may not reliably differentiate between AR and non-AR.

Rhinosinusitis (including nasal polyps) is characterized by two or more symptoms, one of which should be either a) nasal blockage/ obstruction/congestion or b) nasal discharge (anterior/posterior nasal drip). Other symptoms may be c) facial pain/pressure, and/or d) reduction or loss of smell. Discolored nasal drainage may occur in AR and some types of non-AR, so its presence does not necessarily indicate bacterial rhinosinusitis. The common cold from respiratory viruses has an acute onset of rhinosinusitis symptoms typically lasting for less than 10 days or getting better after 5 days. The common cold and rhinosinusitis are not typically associated with nasal itching or ocular symptoms that may be seen in AR.

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TABLE 1

Differential Diagnostic Features of History, Physical Exam, Testing

	Medical History	Physical examination	*In vitro - in vivo* tests
Allergic rhinitis	• Symptoms: obstruction/congestion, nasal drainage, sneezing, itching • Seasonal symptoms may be present with prominent nasal itching and sneezing • Concurrent allergic conjunctivitis (itchy, watery eyes) common • Early onset (age <20 years) common • May be associated with atopic dermatitis, asthma, food allergy, obstructive sleep apnea syndrome	• **Variable appearance of mucosa: mucosal pallor, edema, hyperemia** • **Allergic shiners**: dark discolorations of the periorbital skin • **Dennie–Morgan lines**: folds of the low––er eyelid in children • **Allergic crease**: horizontal wrinkle near the tip of the nose	• Skin-prick tests (SPTs) with allergen • Serum allergen-specific IgE tests • Nasal smears for eosinophils (>10%) (not routinely employed clinically)
Nonallergic rhinitis & infectious rhinosinusitis	• **Idiopathic rhinitis** (**IR**: sneezing, pruritus and ocular involvement uncommon • **NARES,C RSwNP, and atrophic rhinitis**: Hyposmia/anosmia common • **Rhinosinusitis**: headache and facial pain common • **NARES, CRSwNP, and IR**: usually adult onset • **Gustatory rhinitis**: food related symptoms at any age, but more likely with increasing age. Sneezing, pruritus, ocular involvement uncommon. • **Rhinitis of pregnancy**: mainly congestion during the last 6 weeks of pregnancy and up to 2 weeks post-partum	• **Atrophic rhinitis**: mucosal atrophy, foetor, crusts and perceived congestion inconsistent with observed nasal patency • **Rhinosinusitis**: Endoscopic findings of polyps and/or mucopurulent discharge, edema, mucosal obstruction primarily in middle meatus, are prerequisite for diagnosis	• **CRS**: CT findings are a prerequisite for the diagnosis if endoscopic findings inconclusive • **NARES**: Nasal smears for eosinophils (any amount from >5% to >20%) (not routinely employed) • **NARES, atrophic rhinitis and rhinoshinusitis**: Objective and subjective olfactory evaluation to demonstrate hypoosmia/anosmia. • **AERD**: Oral aspirin challenges to demonstrate sensitivity

AERD (aspirin exacerbated respiratory disease); CRSwNP (chronic rhinosinusitis with nasal polyps); IR (idiopathic rhinitis), NARES (nonallergic rhinitis and eosinophilia syndrome)

Modified from Papadopoulos NG, Bernstein JA, Demoly P, Dykewicz M, Fokkens W, Hellings PW, et al. Phenotypes and Endotypes of Rhinitis and Their Impact on Management: A PRACTALL Report. Allergy 2015;70:474-494.

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TABLE 2

Rhinitis differential diagnosis: other disorders	
Structural/Mechanical abnormalities	**Systemic disease**
• **Septal deviation** *Unilateral obstruction, sleep apnea, epistaxis* • **Turbinate hypertrophy** *Often contralateral to septal deviation*	• **Primary ciliary dyskinesia (PCD)** *Recurrent respiratory infections; Kartageners syndrome (situs inversus, chronic rhinosinusitis and bronchiectasis), low nasal and tidally exhaled NO, diagnosis through biopsy and electron microscopy examination of cilia*
• **Nasal tumors** *Epistaxis, hypoosmia/anosmia, facial pain, otalgia, recurrent ear infections, unilateral obstruction* • **Adenoidal hypertrophy** *congestion, mouth breathing, nasal speech and sleep apneic episodes/snoring*	• **Cystic fibrosis** *Thick, viscous secretions, recurrent infection, often radiologic evidence of sinus disease and concurrent nasal polyps. Diagnosis through genetic and sweat testing*
• **Pharyngonasal reflux** *apneic spells, secondary rhinitis (caused by return of ingested liquids) and recurrent pneumonia due to aspiration*	• **Churg–Strauss syndrome** *Asthma, blood eosinophilia, mononeuropathy/polyneuropathy, migratory pulmonary infiltrates, paranasal sinus disease, tissue eosinophilia*
• **Choanal atresia** *Mild symptoms if unilateral, severe symptoms if bilateral (often involving generalized cyanosis*	• **Granulomatosis with polyangiitis** *Obstruction, rhinorrhea, crusting, ulcerations and epistaxis, often secondary bacterial sinusitis*
• **Nasal trauma/foreign object** *May present with unilateral obstruction, epistaxis, olfactory impairment*	• **Sarcoidosis** *Obstruction, nasal crusting, anosmia, epistaxis, lymphadenopathy, malaise*
• **Cerebrospinal fluid rhinorhea** *Clear watery secretion – often unilateral, headaches and olfactory impairment, β-2 transferrin protein elevated in nasal discharge*	• **Amyloidosis** *Obstruction, nasal discharge, epistaxis and post nasal drip* • **Relapsing polychondritis** *Chondritis (auricular, nasal, and laryngotracheal, including ocular inflammation, audio vestibular damage, or seronegative inflammatory arthritis.*

Modified from Papadopoulos NG, Bernstein JA, Demoly P, Dykewicz M, Fokkens W, Hellings PW, et al. Phenotypes and Endotypes of Rhinitis and Their Impact on Management: A PRACTALL Report. Allergy 2015;70:474-494.

2 DIAGNOSIS OF ALLERGIC RHINITIS - RHINOSCOPY AND ENDOSCOPY

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KEY MESSAGES

- Visualizing the nasal cavity is an important evaluation in patients with nasal symptoms
- There are no definitive signs of allergic rhinitis
- Rhinoscopy visualizes the anterior third of the nasal cavity
- Nasal endoscopy visualizes the entire nasal cavity, and allows the differential diagnosis of mucosal vs structural endonasal pathology

One of the great advances in diagnosing and understanding nasal and sinus diseases has been the ability to visualize the entire nasal cavity. The advances primarily relate to the development of ritig and flexible endoscopes.

Traditional approaches of using a nasal speculum and a light source or an otoscope, referred to as rhinoscopy, investigate the anterior part of the nose prior to the level of the middle turbinates. Although the experienced examiner might be able to visualize the middle turbinate with this technique, the view is limited. The anterior part of the nose contains the nasal vestibule, where the epithelium transitions from squamous to pseudostratified columnar ciliated. One can also easily visualize the anterior septum, inferior turbinates, and nasal valve. The nasal valve is formed by the junction between the anterior nasal septum medially and the most caudal margin of the upper lateral cartilage of the nose superiorly and laterally. This valve is the narrowest portion of the airway between the external environment and the alveoli. Deflections of the anterior septum have a marked impact on airflow and can be diagnosed by anterior rhinoscopy.

Other salient findings that can be visualized by rhinoscopy are hypertrophia (Figure 1) or congestion of the inferior turbinates. Most septal perforations involve this area. Large nasal polyps (NP) can also be seen, but novice clinicians often mistake the anterior tip of the middle turbinate or a large inferior turbinate for a polyp. Eighty-five percent of nose bleeds occur in the anterior septum in the area that is the confluence of the anterior ethmoid artery, the facial artery, and the septal artery, which form a rich plexus of vessels, called the Keisselbach's plexus.

There are no definitive signs of allergic rhinitis (AR) on anterior rhinoscopy; however, visualization by rhinoscopy helps to rule out other causes of similar symptoms such as nasal congestion due to anatomic causes.

Although anterior rhinoscopy is helpful, it does not provide visualization of the entire nasal cavity. Specifically it does not provide a good view of the middle meatus, where the sinuses (which are commonly involved in patients with AR) drain. Adenoid hypertrophy, NP, tumors, posterior epistaxis, septal deviations obstructing the sinus ostia, and sinus infections are common and form part of the differential diagnosis of rhinopathy. Nasal endoscopy provides not only visualization to enhance diagnostic abilities (Figures 2, 3 and 4), but also the opportunity to work inside the nose under direct visualization.

Nasal endoscopy can be performed with a rigid or a flexible endoscope. Both can be attached to cameras for educating observers and patients and documenting

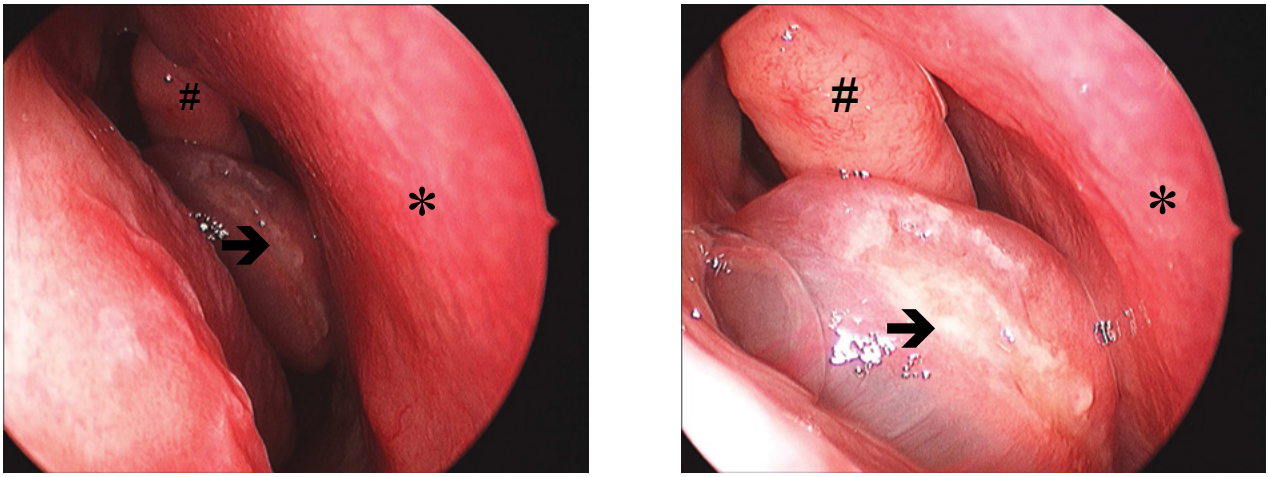

Figure 1 Left panel: Endoscopic view of an antrochoanal polyp (originating from the maxillary sinus and protruding into the nasal cavity) of the right nostril in a teenage male who presented with a unilateral nasal obstruction. Right panel: closeup view. One can see the nasal septum (*), the middle turbinate (#), and the polyp (arrowhead).

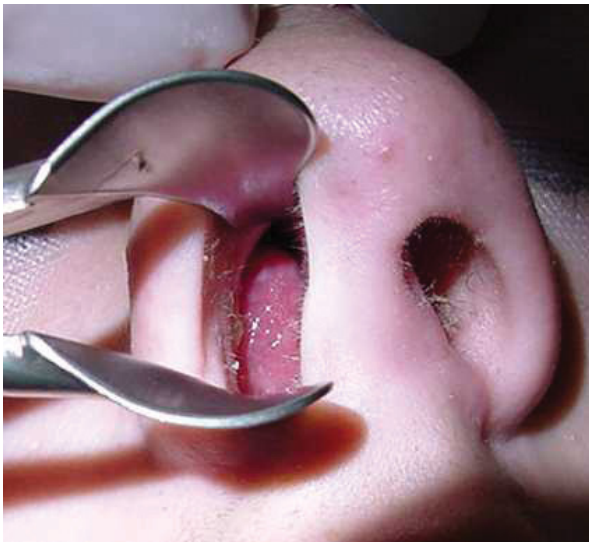

Figure 2 Anterior rhinoscopy with use of a nasal speculum and headlight showing a hypertrophied right inferior turbinate.

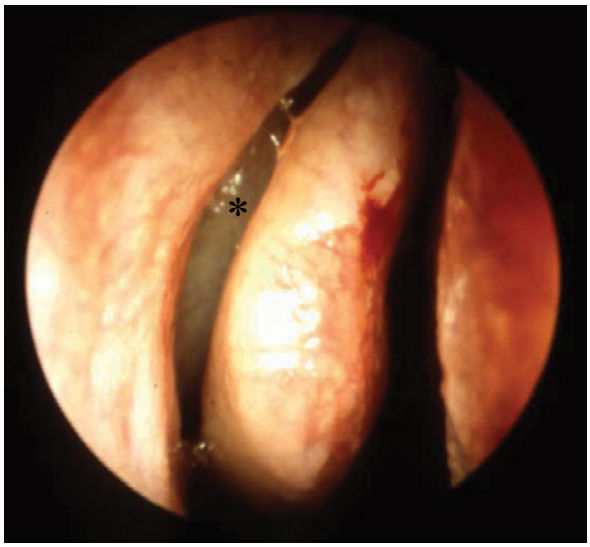

Figure 3 Endoscopic view showing a small polyp (*) in the osteomeatal unit.

the examination. Both examinations are usually performed after the administration of a topical decongestant and anesthetic. The response to the nasal decongestant sometimes provides clues to the underlying problem. Patients with AR often decongest well with oxymetazoline because the congestion of the inferior turbinates is caused by inflammatory mediators released during an allergic reaction that subsequently dilate the cavernous veins in the inferior turbinates.

Flexible endoscopy is easier to perform and can also be used for visualizing the nasopharynx and larynx. Rigid endoscopy provides better image definition, and the endoscope can be held with one hand, freeing the other hand to intervene in the nasal cavity. Such interventions include lysis of adhesions, obtaining guided cultures (Figure 5), performing biopsies, and cauterizing nosebleeds. Directed middle meatal cultures correlate highly with maxillary sinus

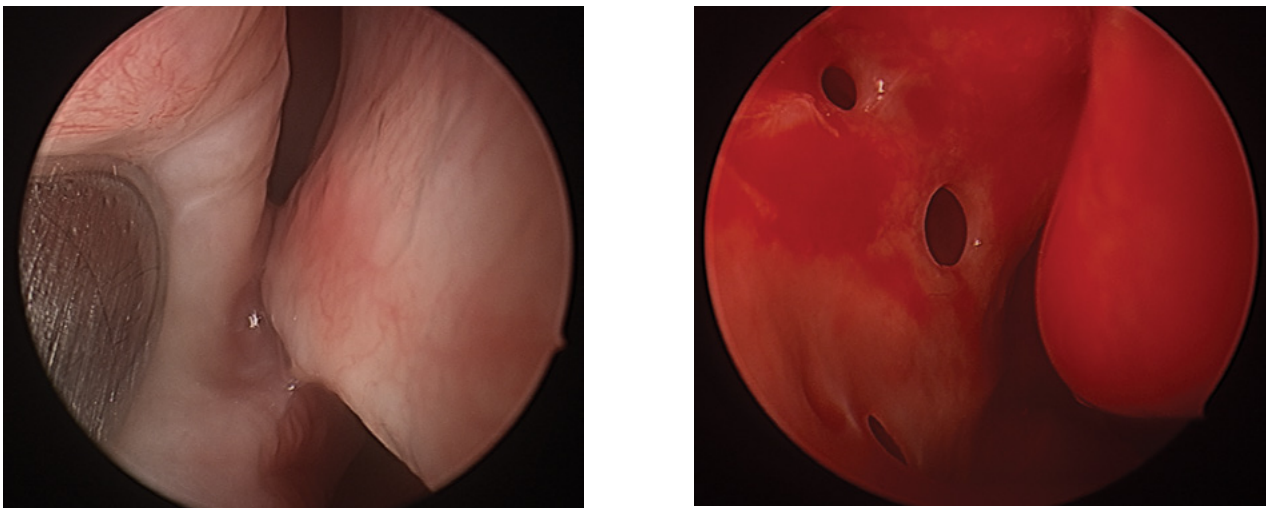

Figure 4 Left panel shows an endoscopic view of a posterior septal deviation impacting the inferior turbinate and heading to the osteomeatal unit. Right panel is an intraoperative photo following removal of the septal deviation showing multiple accessory ostia believed to be secondary to prior acute infections.

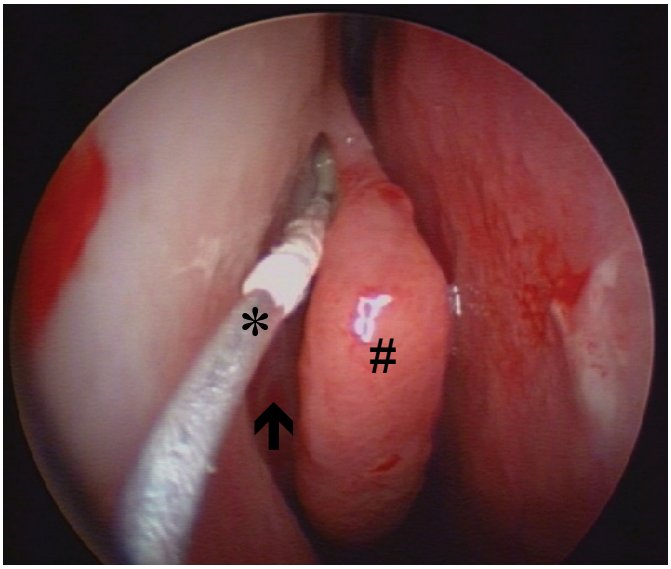

Figure 5 View of the right middle turbinate (#) and the right osteomeatal unit (arrowhead) with some purulent drainage. This view was obtained with the use of a rigid scope, allowing the introduction of a Calgae swab (*) to obtain a culture.

puncture cultures in patients with acute bacterial rhinosinusitis.

When should nasal endoscopy be performed in a patient who has a nasal complaint? One could argue that it should be done in everyone, but that would be too costly. A more reasonable approach is to perform endoscopy in subjects who have symptoms that are not explained by rhinoscopy and who did not respond to initial treatment.

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3 NON-INVASIVE EVALUATION OF NASAL INFLAMMATION (NO, NASAL CYTOLOGY AND MEDIATORS)

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KEY MESSAGES

- Allergic rhinitis (AR) is a complex allergen-driven mucosal inflammation caused by the interplay between local and infiltrating inflammatory cells and many vasoactive and inflammatory mediators
- Increased Nasal Nitric Oxide (nNO) levels are associated with nasal inflammation; however, results should be interpreted with caution in patients with severe or persistent AR, which may reduce nNO levels
- Nasal cytology is performed to help differentiate AR (predominantly) from infectious rhinitis (predominantly neutrophils), although it is relatively nonspecific and insensitive
- Non-invasive sampling of mediators by nasal lavage is an emerging method to monitor AR

In allergic rhinitis (AR), the early-phase reaction due to IgE-mediated mast cell degranulation and mediator release is rapid and leads to sneezing and rhinorrhea. The late-phase reaction involves an eosinophilic infiltrate, leading to nasal inflammation.

Nasal nitric oxide (nNO) is produced continuously in the paranasal sinuses without inflammatory stimuli and plays a role in airway homeostasis. AR may be associated with elevated nNO levels, by the increase in inducible nitric oxide synthase (iNOS) expression in respiratory epithelial cells. While the level of nNO may be increased by nasal inflammation, nasal swelling and secretions may occlude the ostia of the paranasal sinuses thereby lowering nNO levels. A high nNO may be a useful marker of eosinophilic inflammation of the nasal cavity and indicate open sinus ostia. nNO measurements may be an alternative to diagnose AR in patients who are not able to undergo allergic tests or invasive procedures.

Infiltrating eosinophils are the hallmark of nasal inflammation in AR. Nasal smears for eosinophils are not recommended for routine use in diagnosing AR when the diagnosis is clearly supported, but may be a useful adjunct when there remains a high clinical suspicion of allergy in a history-positive, skin test-negative patient. Nasal cytology can not only be utilized to establish the diagnosis of AR, but is also useful in the follow-up of treated patients with this condition. The technique allows clinicians to detect the cellular modifications of the nasal epithelium during allergen exposure (Figure 1) and by subsequent treatment with corticosteroids.

Many different mediators, cytokines, and chemokines have been measured in nasal lavage (NL) studies (Figure 2). Certain proinflammatory mediators including eosinophilic major basic protein and neutrophil elastase have been identified in allergic mucin. Eosinophil cationic protein (ECP) is one of the most studied inflammatory markers and is considered a general marker of mucosal inflammation, both in processes of eosinophil and neutrophil activation. Another key feature of mucosal inflammation is the exudation of plasma proteins such as albumin, a2-macroglobulin, and others, which can be monitored by analysis of plasma proteins in NL. While histamine is rapidly degraded by

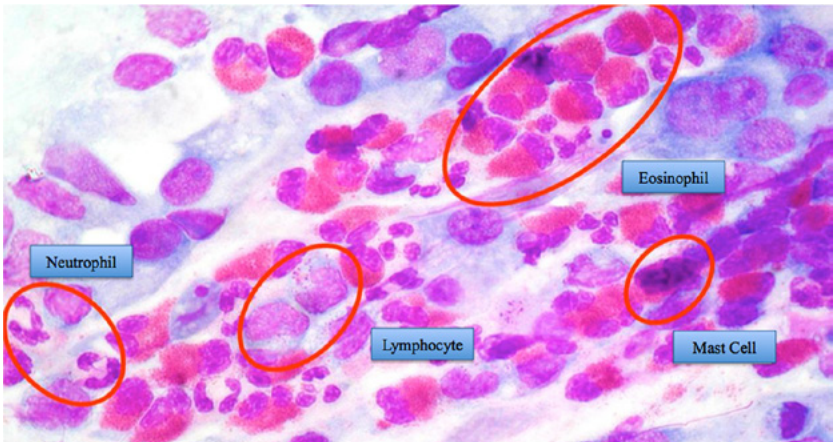

Figure 1 Nasal inflammation occurring in seasonal allergic rhinitis. (From *Gelardi M, Luigi Marseglia G, Licari A, Landi M, Dell'Albani I, Incorvaia C, et al. Nasal cytology in children: recent advances. Ital J Pediatr 2012;25;38:51.*)

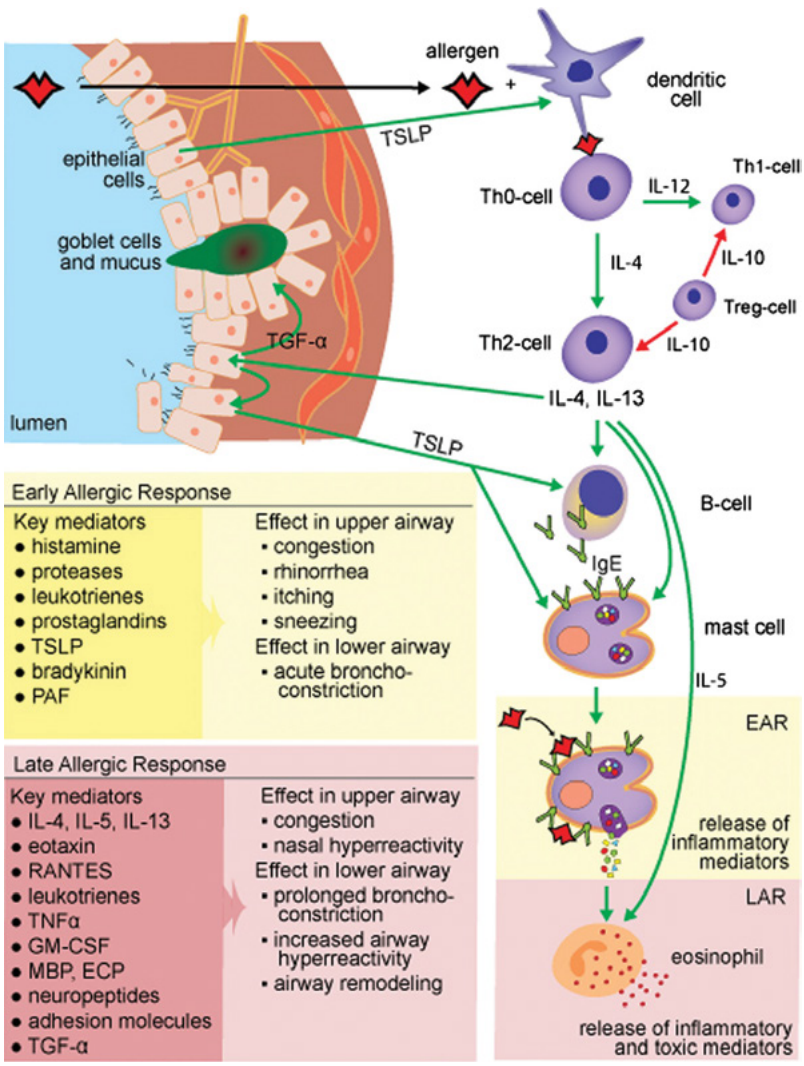

Figure 2 Biomarkers of allergic rhinitis. (*Reprinted from Pulm Pharmacol Ther, 23/6, Diamant Z, Boot JD, Mantzouranis E, Flohr R, Sterk PJ, Gerth van Wijk R. Biomarkers in asthma and allergic rhinitis, 468-481, Copyright 2010, with permission from Elsevier.*)

histaminases and N-methyl transferase, the more stable mast cell degranulation products, tryptase and prostaglandin PGD2 are recommended as markers of mast cell activation. The choice of which inflammatory marker to probe in AR depends on the purpose of the investigation and the manner of monitoring therapy.

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4 SKIN TESTING IN THE DIAGNOSTIC WORKUP OF RHINITIS

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Skin testing is well established in the diagnostic work-up of allergic rhinitis (AR) to demonstrate IgE mediated sensitizations. It is mainly performed with protein allergens and only rarely with small molecules. A positive skin test usually indicates sensitization but not necessarily clinically relevant allergy. The latter has to be proven either by a very convincing history or with further steps in the algorithm of *in vivo* diagnosis (i.e. nasal challenge tests).

KEY MESSAGES

- Skin testing with allergen extracts or small molecules is well established in the diagnostic work-up of allergic rhinitis (AR) to demonstrate IgE mediated sensitizations
- The quality of allergen extracts is critical. False negative results can occur if minor allergens or instable allergenic proteins are underrepresented in an extract
- Well-standardized allergen extracts are available for many inhalant allergens
- The best established skin test is the skin prick test (SPT). The more sensitive intradermal tests are recommended after negative SPT in some situations, but can lead to false positive reactions and are associated with a higher risk of systemic side effects

SKIN PRICK TEST

The skin prick test (SPT) is the best established skin test and recommended as first diagnostic test in patients with AR. SPT can be performed in patients of any age although the reactivity may possibly be lower in the elderly. The quality of allergen extracts used for SPT is critical. False negative results can occur if minor allergens or instable allergenic proteins are underrepresented in an extract. However, well-standardized allergen extracts are available for many inhalant allergens. EU legislation makes it currently difficult to have new and optimized diagnostic products approved due to very high standard requirements.

The major advantage of SPT as compared to an *in vitro* measurement of specific IgE antibodies is the fact that the test can be interpreted within 15 to 20 minutes (Figure 1). A further advantage is that the test gives a visual indication of the sensitivity to the patient which may have impact on the patient's behavior. Usually prick tests are performed with panels of allergens of interest; a standard set is proposed for inhalant allergens (Table 1).

Some studies show discordances between serum-specific IgE and SPT results. In a recent meta-analysis on studies with SPT with inhalant allergens, every fourth sensitized patient would have been misdiagnosed as non-sensitized for a particular allergen if only serum specific IgE testing had been done. This has leads to the suggestion that the two methods complement each other and cannot be used interchangeably.

OTHER SKIN TESTS

Intradermal tests are recommended after negative SPT in some clinical situations. They are considered to be more sensitive than the SPT but can lead to false positive reactions and they are associated with a higher risk of sys-

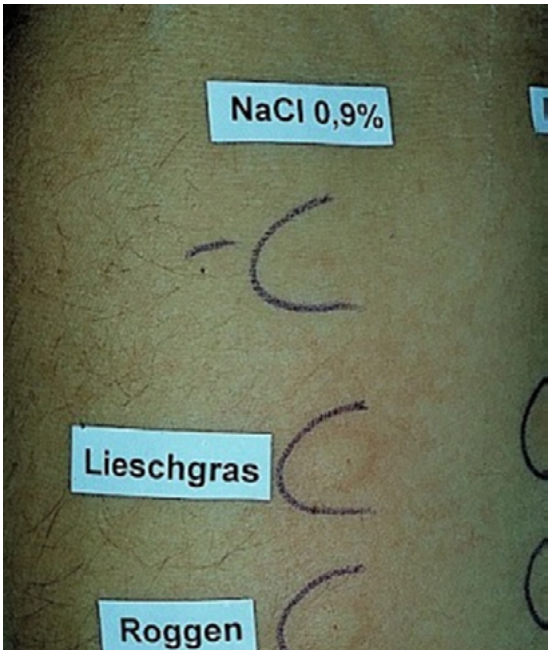

Figure 1 SPT is usually performed on the forearm with a negative (saline 0.9%) and positive (histamine 10mg/ml) control. A reaction is considered to be positive with a wheal diameter ≥ 3mm after 15 minutes.

TABLE 1

Proposal for a standard prick test panel for Europe for inhalants	
Hazel	*Corylus avellana*
Alder	*Alnus incana*
Birch	*Betula alba*
Plane	*Platanus vulgaris*
Cypress	*Cupressus sempervirens*
Grass mix	*Poa pratensis, Dactilis glomerata, Lolium perenne, Phleum pratense, Festuca pratensis, Helictotrichon pretense*
Olive	*Olea europaea*
Mugwort	*Artemisia vulgaris*
Ragweed	*Ambrosia artemisiifolia*
	Alternaria alternata (tenuis), Cladosporium herbarum, Aspergillus fumigatus
	Parietaria
Cat	
Dog	
	Dermatophagoides pteronyssinus, Dermatophagoides farinae,
Cockroach	*Blatella germanica*

temic side effects. Therefore extracts utilized for intradermal skin testing are less concentrated than those utilized for SPT.

Patch testing is the mainstay in the diagnosis of allergic contact dermatitis – it is not recommended for the diagnosis of AR.

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5 PROVOCATION TESTS

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KEY MESSAGES

- Nasal provocation involves a controlled exposure of the nasal mucosa to allergen(s) or non-specific triggers in order to elicit a measurable response
- Provocations have been essential in delineating patho-mechanisms of (allergic) rhinitis
- Applications in clinical practice include identification of predominant allergens in polysensitised patients, proof of causation of symptoms for novel or occupational allergens, and investigation of local allergic rhinitis
- Several different approaches to provocation exist, universal consensus on optimal methods is lacking

Nasal provocation testing is the use of various stimuli – typically specific allergen(s), but also non-specific triggers including irritants, chemicals and physical stressors – to elicit a measurable response from the nose. Outcomes include symptom scores, measures of nasal airway patency, cellular influx and inflammatory mediators in nasal fluid.

Applications of provocation tests are outlined in Table 1. In clinical practice, provocations may help differentiate between sensitisation and allergy, and identify individuals with local allergic rhinitis (AR). In research settings, provocations have demonstrated the efficacy of pharmacotherapies including anti-histamines and intranasal corticosteroids, and identified basic immunological and neural mechanisms.

A reliable, reproducible means of delivering allergen to the nasal mucosa is required. Various delivery systems used are outlined in Table 2, alongside different provocation protocols. The latter include up-dosing/titration provocations, providing dose-response profiles and allowing tailoring of future doses to each individual. Repeat challenges, usually every 24 hours for several days, may provide an approximation to real-life allergen exposures and allow investigation of 'priming' of the mucosa.

For research, participants are selected on the basis of typical allergic symptoms and evidence of systemic sensitisation to the allergen in question. Allergen provocations are usually performed outside of usual seasonal exposure and in the absence of symptoms induced by alternative/perennial allergens, infection, nasal polyps or structural pathologies. Whilst provocations are extremely safe, individuals with poorly controlled asthma or FEV1 <70% predicted should be excluded; other contraindications include pregnancy or a history of anaphylaxis to the allergen in question. Anti-allergic medications need to be stopped for a sufficient wash-out period prior to provocations.

Clinical and laboratory outcomes of nasal provocations are given in Table 3. Typically, provocation is preceded by nasal lavage to provide a clean baseline. An example of the time-course of symptom and peak nasal inspiratory flow responses to a single dose nasal allergen challenge is given in Figure 1. In contrast to bronchial allergen provocation, a distinct late phase response is seldom seen, although nasal obstruction typically persists for some hours after provocation. Conversely, clear immunological

TABLE 1

Clinical and research uses of nasal provocations

Clinical Practice	Research
Confirmation of clinical relevance in cases of polysensitisation to aeroallergens	Assessment of mechanisms of (allergic) rhinitis: • Cellular influx • Early and late phase mediators • Neural pathways • Gene expression • Naso-ocular, naso-bronchial interaction
Selection of patients for allergen immunotherapy (e.g. for house dust mite)	
Investigation of symptoms in the absence of evidence of systemic allergen sensitisation (local allergic rhinitis)	
Proof of symptom causation for novel and occupational allergens	Assessment of therapeutic interventions: • Efficacy • Onset • Duration
Investigation of aspirin hypersensitivity	
Assessment of non-specific nasal hyperreactivity	

TABLE 2

Methods of nasal allergen provocation

Delivery System	Challenge Protocol
Allergen in aqueous solution, administered by nasal spray, drops, pipette	Up-dosing/titration protocol - half-log increments, every 10 minutes, ending at maximum dose or threshold response
Filter discs with adsorbed allergen, placed directly onto nasal mucosa	
Allergen as dry powder insufflated or nebulised	Single fixed dose challenge (standard or determined by titration challenge)
Allergen administered in high volume nasal lavage	Repeat dosing, usually daily, to mimic seasonal priming effect

TABLE 3

Clinical and laboratory outcome measures of nasal provocation.

Clinical Outcomes	Laboratory Outcomes
Total nasal symptom score: 0-3 for each of sneezing, rhinorrhoea, itching, blocking/congestion; maximum score 12.	Nasal mucosal fluid, collected by lavage or direct absorption (synthetic filters, polyurethane sponges), immunoassay for: • Early phase mediators, e.g. tryptase, histamine, leukotrienes • Cytokines and chemokines • Allergen-specific antibodies • Eosinophil products, e.g. ECP • Neuropeptides • Vascular, glandular proteins
Visual analogue scale (0-100mm; none – maximal symptoms)	
Collected secretion weight	
Nasal airflow/patency: • Peak inspiratory flow • rhinomanometry	
Nasal cross-sectional area: • acoustic rhinometry	Nasal brushings for cytology, mRNA
Eosinophilic inflammation: • nasal FeNO	Nasal (turbinate) biopsy for immunohistochemistry, in situ hybridisation
	Nasal lavage for cytology

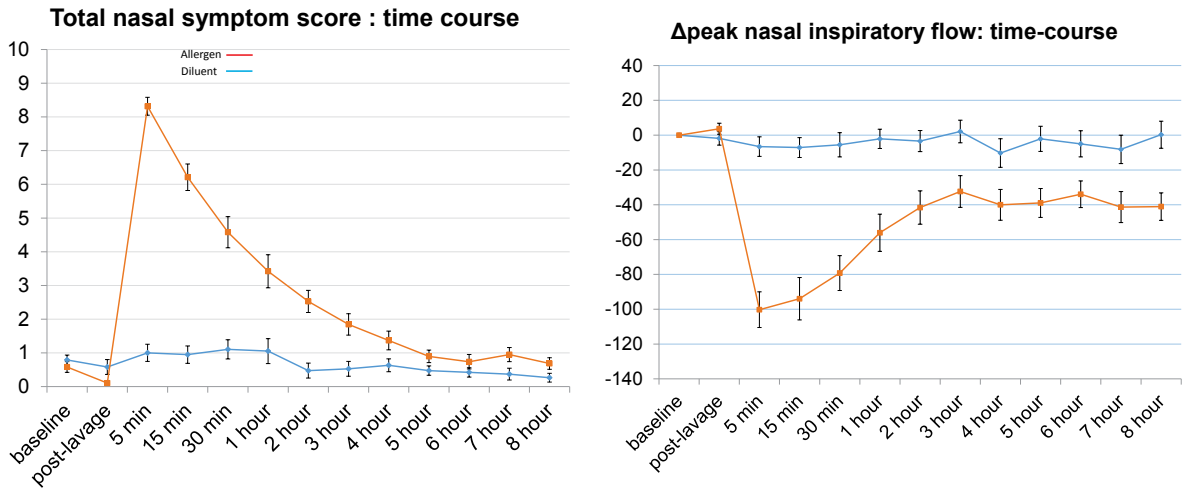

Figure 1 Time course of total nasal symptom score (0-12) and change from baseline peak nasal inspiratory flow (L/min) in 19 cat-allergic individuals after single dose cat allergen challenge and diluent-only challenge. (*Adapted from Scadding GW, Eifan A, Penagos M, et al. Local and systemic effects of cat allergen nasal provocation. Clin Exp Allergy 2015;45:613-623.*)

TABLE 4

Non specific nasal challenges		
Biochemical	**Irritant/inflammatory**	**Physical**
Histamine – ipsilateral and contralateral effects	Capsaicin - Activates TRPV-1 receptors on sensory nerve endings; increased response in allergic rhinitics	Cold dry air - rhinorrhoea and congestion in susceptible individuals, associated with increased histamine, PGD2 and kinins. Superior to histamine in identifying patients with non-allergic rhinitis from controls.
Methacholine – ipsilateral effect only		
AMP – non-specific mast cell activation	Environmental tobacco smoke - rhinitis in susceptible individuals	
Neuropeptides – stimulation of sensory nerves	Diesel exhaust particles – may augment response to allergen	
Bradykinin, leukotrienes – investigation of effects of individual components of mast cell granules	Ozone (in challenge chamber) - neutrophilic inflammation	Hyperosmolar solutions, e.g. mannitol, hypertonic saline - induces fluid shift into the nasal lumen and increases in mediators including mast cell, epithelial and neuronal factors.
Aspirin – diagnosis of hyperreactivity and desensitisation	Chlorine – increases in nasal resistance	

late phase responses are seen for both cellular influx (eosinophilic) and nasal fluid cytokines/chemokines (Th2 predominant).

Whilst allergen provocations are more frequently used, non-specific provocations, described in Table 4, have also been used to identify nasal hyperreactivity, investigate the effect of environmental pollutants, and elucidate basic mechanisms of rhinitis.

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6 SPECIFIC IgE AND DIAGNOSIS OF ALLERGIC RHINITIS

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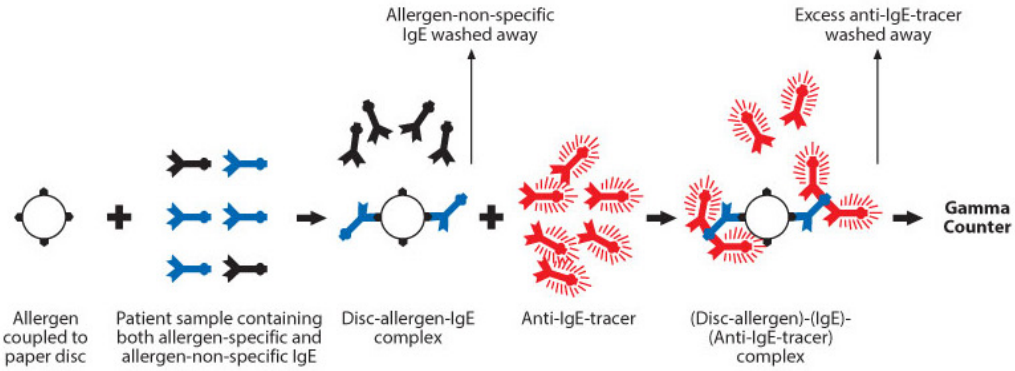
KEY MESSAGES

- Elevated allergen-specific IgE serum levels are indicative for an allergy
- Determination of allergen-specific IgE in serum allows rapid screening of the sensitization spectrum of a patient
- Screening panels of allergen-specific IgE without previous consideration of the history of the patient is not recommended
- A negative skin prick or serum IgE test does not entirely exclude a diagnosis of AR especially if they are in contrast with a convincing clinical history
- The diagnosis of AR with discordant clinical history and elevated allergen-specific serum IgE levels needs to be confirmed by provocation tests

Allergic rhinitis (AR) is a very common inflammatory chronic condition affecting the upper airways. It occurs in predisposed individuals when allergens such as pollens, dust, or animal dander are inhaled. Its incidence is rising in parallel with other IgE-mediated diseases, affecting 10 to 30% of adults and up to 40% of children in industrialised countries. Seasonal AR is mainly elicited by exposure to pollens during the pollination period, while perennial AR is elicited by allergens present in the environment throughout the year like those from house dust mite allergens or fungal spores. The disease is often associated with other IgE-mediated diseases like allergic asthma, or atopic dermatitis. The characteristic symptoms of AR are excess nasal secretion, itching, sneezing, nasal congestion and obstruction associated with eosinophilic inflammation of the mucosa. To confirm the diagnosis of AR, sensitisation (specific IgE reactivity) needs to be recorded and should be concordant with the clinical history.

The prototype for the in vitro detection of serum IgE (the radioallergosorbent test, RAST) first described in 1967 used a paper disc as a solid phase to covalently immobilize the allergen followed by the addition of patient's serum. After different washing procedures to remove unbound serum proteins and antibodies, bounded IgE was detected with 125I-labelled polyclonal anti-human IgE (Figure 1). Modern assays for the detection of allergen-specific IgE have undergone impressive improvements including the calibration against the WHO Standard 72/502, allowing quantitative determinations, and the implementation of fully automated devices (Figure 2). To date the most commonly used system to determine allergen-specific IgE is the ImmunoCAP system (Thermo Fisher Scientific, Uppsala) considered as the "gold standard" for the in vitro diagnosis of allergic conditions. More recently, novel diagnostic tests based on allergen microarrays have been introduced both in research and clinical practice. Multiplex-based in vitro tools for allergy diagnosis allow a component resolved diagnostics of the atopy status of a patient in a cost effective way.

In vitro tests for allergen-specific serum IgE are excellent for identifying a sensitization state of a patient and can be recommended at any age and without wash-out for antiallergic medication. How-



F/N MODIFIED RAST SCORING SYSTEM

CLASS	COUNTS
0	Less than 500
0/I	500–749
I	750–1600
II	1601–3600
III	3601–8000
IV	8001–18000
V	18001–40000
VI	40001+

Figure 1 Mechanism of the first radioallergosorbent assay (RAST).

Figure 2 Example of a fully automated device for the determination of allergen-specific IgE (Phadia™ Immunoassay Analyzer).

ever, a positive *in vitro* test for allergen-specific IgE in serum does not always equate with clinical allergy, and a negative test does not completely exclude the disease. For a clinical manifestation of any allergy the only biologically relevant allergen-specific IgE is those immobilized on the surface of effector cells through the high affinity FcεRI receptors. This can, through cross-linking of the IgE molecules after allergen exposure and the resulting mediator release from effector cells, elicit local symptoms of AR also in the absence of soluble allergen-specific IgE in serum. Therefore, the best tool for the diagnosis of AR is by correlating the patient's history and physical exam with the presence of aeroallergen specific IgE determined by skin testing or by *in vitro* assays. Like skin testing, limitations of *in vitro* specific IgE measurement include the availability of fully standardized allergenic extracts, particularly for foods, drugs, and occupational agents.

New perspectives for the diagnosis of AR have been opened by *in vitro* diagnostic tests based on molecular approaches, which allow a component resolved diagnosis of hundreds of the offending allergens. Multiplex measurement platforms like the Immuno-Solid phase Allergen Chip (ISAC) allows discrimination between genuine and cross-reactive sensitization thereby reducing unnecessary allergen challenges, and facilitating the identification of patients with a good prognosis for a successful allergen immunotherapy.

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7 COMPONENT RESOLVED DIAGNOSIS

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KEY MESSAGES

- The IgE response usually evolves from a monomolecular to an oligo- and poly-molecular stage ("molecular spreading" phenomenon) and can involve both, highly specific and highly cross-reactive molecules
- Allergic patients reacting to the same allergenic source (e.g. grass pollen) can be highly different in their molecular profile of IgE sensitization to that allergenic source
- Component resolved diagnosis (based on single or multiplex assays) allows discriminating whether a patient is truly or only apparently sensitized to an allergenic source (e.g. pollen)
- Component resolved diagnosis has a strong impact on the precision of allergen immunotherapy (AIT) prescription, which might imply to a better AIT efficacy and cost-effectiveness. *Ad hoc* Diagnostic Algorithms have been proposed

The number of allergenic molecules cloned and available for diagnostic tests grows year after year. We can nowadays precisely define the patient's IgE repertoire and distinguish, in polysensitized patients, true sensitization (IgE to major, "species-specific" allergenic molecules) from apparent sensitization, due to cross-reactive molecules (e.g. profilin, serum albumin, tropomyosin, CCD) shared by many allergenic sources.

This molecular approach, also called 'component-resolved diagnosis' (CRD), can rely upon classical 'singleplex' or newer 'multiplex' methods. By the singleplex method, single molecules are separately analyzed and the operator can select, with an inductive approach, those to be tested in the individual patient. By the multiplex method, fixed arrays of molecules are tested in the same assay and the response is interpreted with a deductive approach.

CRD applies to all IgE-mediated allergic diseases and it is of paramount importance in the correct diagnosis of pollen-food syndromes. In patients with seasonal allergic rhinitis (SAR), CRD may influence therapeutic decisions, by helping the selection of sources for allergen immunotherapy (AIT). Indeed, the IgE response against grass pollen (e.g. *Phleum pratense*) usually evolves from a simple, monomolecular stage to an oligomolecular stage and eventually to a polymolecular sensitization stage. This phenomenon has been defined as 'molecular spreading', that is, "The sequential development of antibody (IgE) response to distinct non-cross-reacting molecules from the same antigenic (allergenic) source, starting with an "initiator" (allergenic) molecule." Phl p 1 is the probable 'initiator' molecule in most patients, and the response involves then Phl p 4 or Phl p 5, thereafter also Phl p 2 and Phl p 11 and at a later stage Phl p 12 or Phl p 7 (Figure 1). Interestingly, the molecular spreading process follows different sequences in different children: some patients remain sensitized only to the "initiator" molecule while a few patients become sensitized to most or all allergenic molecules. Consequently, a population of grass-pollen allergic patients "apparently" homogeneous if examined with an allergen extract, is

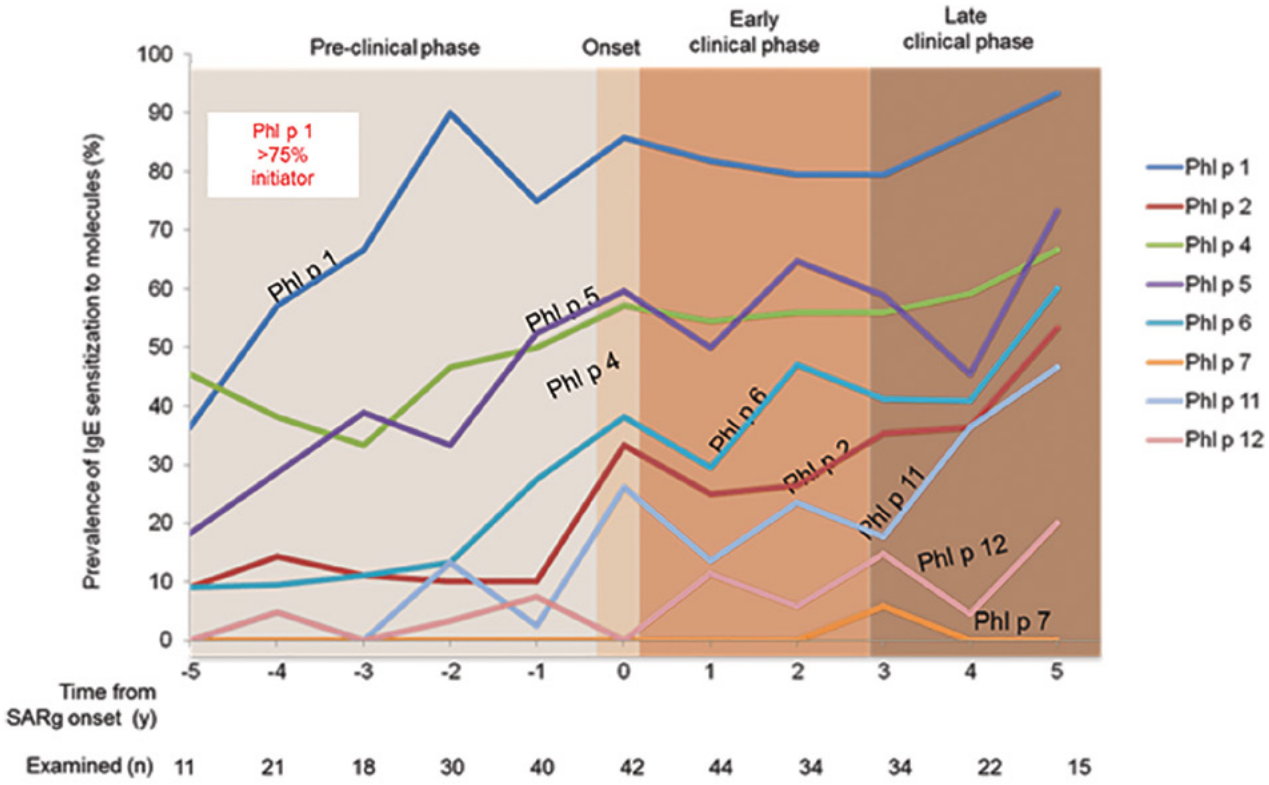

Figure 1 IgE to Phleum pratense allergenic molecules from the onset of grass-related seasonal allergic rhinitis (SAR). Lines show the prevalence of IgE sensitization (ISAC class >_1) to the 8 Pheum pratense allergenic molecules in children whose sera were available at each time point. The number of children examined at each time point is indicated under the x-axis. Clinical stages of SAR are also indicated. *(Adapted from J Allergy Clin Immunol 130/4, Hatzler L, Panetta V, Lau S, et al. Molecular spreading and predictive value of preclinical IgE response to Phleum pratense in children with hay fever. 894-901. e5, Copyright 2012, with permission from Elsevier.)*

remarkably heterogeneous when examined with allergenic molecules (Figure 2).

A consistent proportion of pollen allergic patients are sensitized to profilin and other highly cross-reacting molecules. When tested with extracts-based skin prick tests or IgE assays, these patients with SAR appear sensitized to many different pollens which often share, especially at warmer latitudes (e.g. Mediterranean countries), overlapping season. *In vitro* molecular assays can discriminate true IgE sensitization from co-recognition and allow refining the diagnosis made with extract-based SPT or IgE assays. Not surprisingly, a precise molecular diagnosis can play a strong influence on AIT prescription in Mediterranean countries (Figure 3) and this might imply a better AIT efficacy and cost-effectiveness. Accordingly, new diagnostic algorithms for an improved prescription of AIT in patients with pollen-related allergic rhinitis have been recently proposed (Figure 4).

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Profile APCS code	profile's binary code (8 molecules): cut-off 0.35 kU/L	rPhl p 1	rPhl p 2	rPhl p 4	rPhl p 5	rPhl p 6	rPhl p 7	rPhl p 11	rPhl p 12	n pos. mol.	n	%	cum. %
128	10000000	●								1	36	20,8	21
248	11111000	●	●	●	●	●				5	21	12,1	33
160	10100000	●		●						2	10	5,8	39
184	10111000	●		●	●	●				4	8	4,6	43
186	10111010	●		●	●	●		●		5	8	4,6	48
251	11111011	●	●	●	●	●		●	●	7	8	4,6	53
192	11000000	●	●							2	7	4,0	57
216	11011000	●	●		●	●				4	7	4,0	61
249	11111001	●	●	●	●	●			●	6	7	4,0	65
250	11111010	●	●	●	●	●		●		6	7	4,0	69
32	100000			●						1	5	2,9	72
224	11100000	●	●	●						3	5	2,9	75
152	10011000	●			●	●				3	4	2,3	77
185	10111001	●		●	●	●			●	5	4	2,3	79
208	11010000	●	●		●					3	3	1,7	81
218	11011010	●	●		●	●		●		5	3	1,7	83
48	110000			●	●					2	2	1,2	84
64	1000000		●							1	2	1,2	85
144	10010000	●			●					2	2	1,2	86
162	10100010	●		●				●		3	2	1,2	87
187	10111011	●		●	●	●		●	●	6	2	1,2	88
193	11000001	●	●						●	3	2	1,2	90
217	11011001	●	●		●	●			●	5	2	1,2	91
225	11100001	●	●	●					●	4	2	1,2	92
16	10000				●					1	1	0,6	92
34	100010			●				●		2	1	0,6	93
58	111010			●	●	●		●		4	1	0,6	94
96	1100000		●	●						2	1	0,6	94
129	10000001	●							●	2	1	0,6	95
130	10000010	●						●		2	1	0,6	95
132	10000100	●					●			2	1	0,6	96
156	10011100	●			●	●	●			4	1	0,6	97
188	10111100	●		●	●	●	●			5	1	0,6	97
194	11000010	●	●					●		3	1	0,6	98
232	11101000	●	●	●		●				4	1	0,6	98
240	11110000	●	●	●	●					4	1	0,6	99
254	11111110	●	●	●	●	●	●	●		7	1	0,6	99
255	11111111	●	●	●	●	●	●	●	●	8	1	0,6	100
0	0									0	3	1,7	

Figure 2 Profiles of IgE sensitization to eight Phleum pratense molecules in 176 sensitized children. Profiles of IgE sensitization to eight Phleum pratense molecules in 176 children with an IgE reaction to Phleum pratense and complete data-set. The APCS code and the absolute and cumulative frequency are shown. The profiles are ordered by declining frequency and the point at which the arbitrary threshold of 80% of the patient population has been reached is marked in red. (*Reprinted from J Allergy Clin Immunol, 129/3, Tripodi S, Frediani T, Lucarelli S, et al. Molecular profiles of IgE to Phleum pratense in children with grass pollen allergy: implications for specific immunotherapy. 834-839.e8, Copyright 2012, with permission from Elsevier.*)

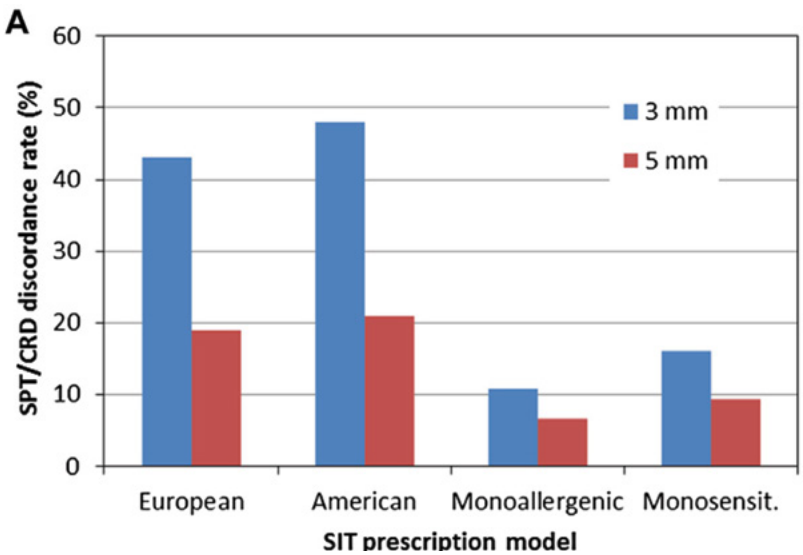

Figure 3 The impact of CRD on AIT prescription. CRD impact on AIT prescription based on SPT with extract, by SPT cut-point and prescription model. (*Reprinted from J Allergy Clin Immunol, 134/1, Stringari G, Tripodi S, Caffarelli C, et al. The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. 75-81, Copyright 2014, with permission from Elsevier.*)

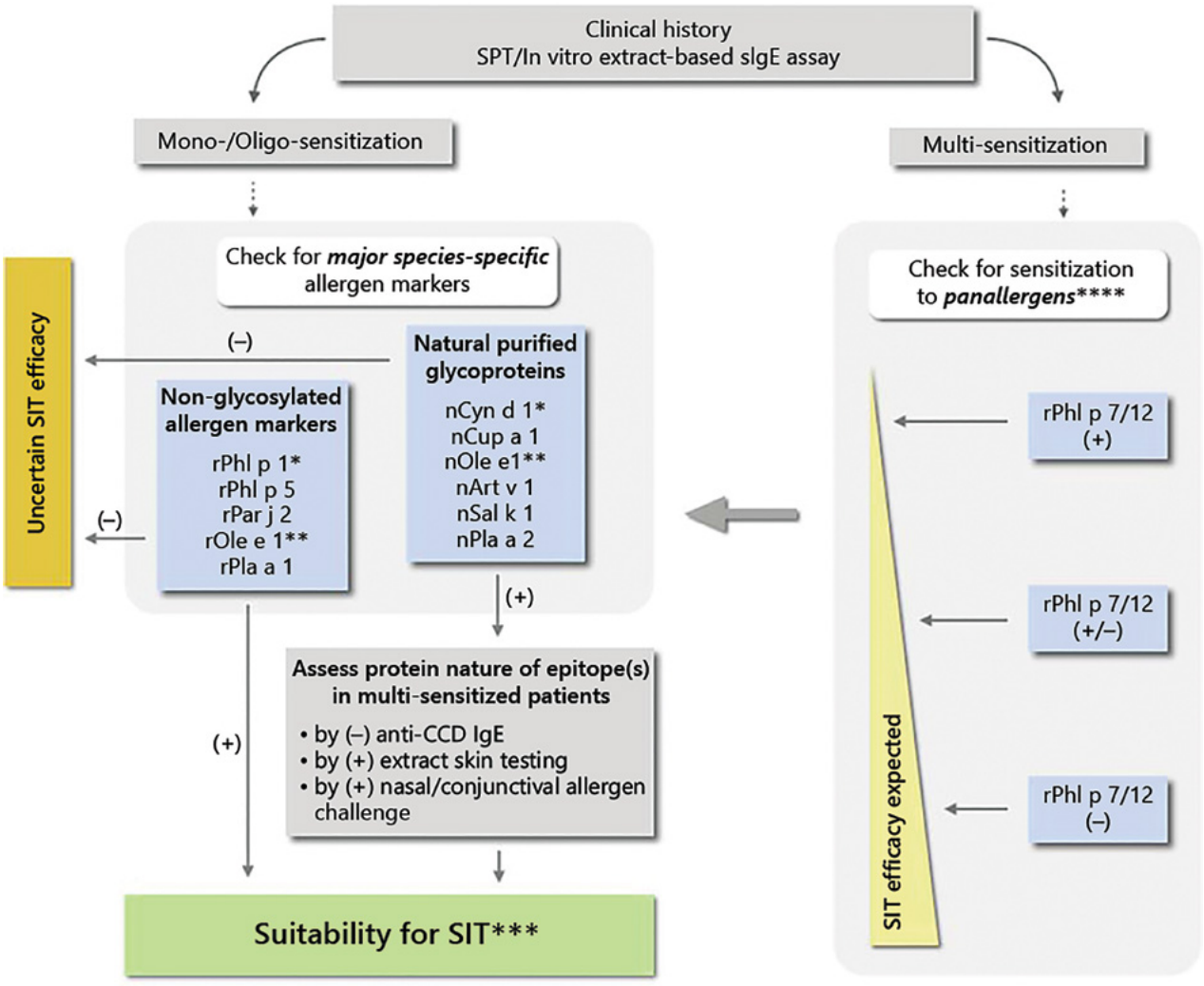

Figure 4 Proposal for a basic CRD work-up for pollen AIT candidates in southern Europe. For the purposes of the current figure, component allergens' names denote the detection of corresponding specific IgE. * In cases with nCyn d 1 (+) > rPhl p 1 (+) and negative species-specific allergen markers for Timothy grass (e.g. rPhl p 2, rPhl p 5 and rPhl p 6), a Bermuda grass standardized extract may be sufficient for the treatment of clinical allergy to grass pollen (please refer to text). ** Both natural nOle e 1 and recombinant rOle e 1 are commercially available in Europe. *** For optimal AIT efficacy, the use of standardized extracts containing the species-specific major allergen at high-dose concentration may be required. **** rPhl p 7, as a polcalcin marker and rPhl p 12, as a profilin marker are typically used. In areas with a high prevalence of birch pollen allergy (not typical of the Mediterranean region), rBet v 4 and rBet v 2 may respectively be used, along with the essential rBet v 1 birch pollen major allergen. (*Reproduced with permission from Douladiris N, Savvatianos S, Roumpedaki I, et al. A molecular diagnostic algorithm to guide pollen immunotherapy in southern Europe: towards component-resolved management of allergic diseases. Int Arch Allergy Immunol 2013;162:163–172; with permission from Karger Publishers.*)

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8 DIAGNOSIS OF ALLERGIC RHINITIS - CELLULAR TESTS

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KEY MESSAGES

- Allergic rhinitis (AR) symptoms are significantly associated with allergen specific basophil sensitivity. Evaluation of cellular allergen sensitivity may be a useful tool for mirroring clinical allergen sensitivity
- The basophil activation test (BAT) is considered as an effective *in vitro* diagnostic test to identify difficult allergic cases and also can be used in monitoring immunotherapy
- Flow cytometry to measure basophils that express activation markers, including CD63, CD203c or both have been proven to be a useful tool for the assessment of the immediate response to allergens mediated by IgE
- BAT also might be used in the diagnosis of local AR

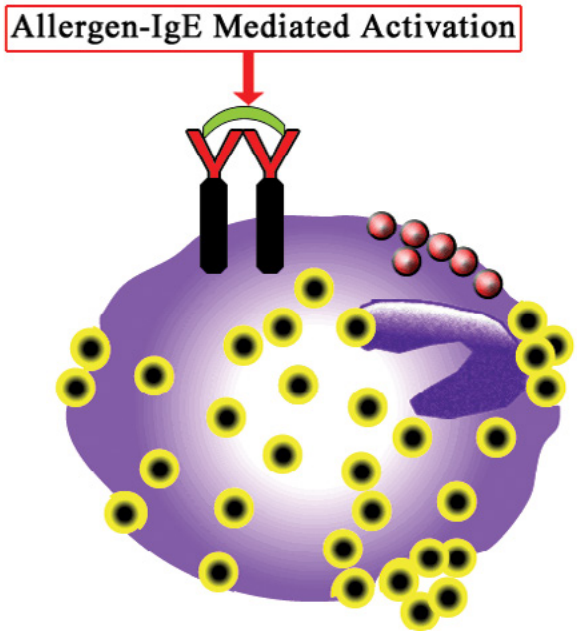
Cellular allergy tests are used to diagnose and follow up allergic diseases. They have advantages of detecting antigen-dependent cellular processes without any risk to the patient. Several studies also support its usefulness in monitoring allergen immunotherapy (AIT).

Allergic rhinitis (AR) symptoms are significantly associated with elevated basophil sensitivity. Evaluation of allergen-specific basophil sensitivity could be a useful tool for distinguishing allergic sensitisation. Effector cell based *in vitro* tests might help in defining the allergic state in sensitized individuals.

The most common cellular test is basophil activation by allergen (BAT). BAT evaluating histamine, sulfidoleukotriene and cytokine release upon allergen exposure has been used in the diagnosis of allergy for many years (Figure 1). However, the measurement of allergen-induced histamine release from patient's basophils can not be used widely, because it is expensive and time consuming. In recent years, flowcytometric analysis based on the detection of allergen-induced basophil surface markers has been used (Figure 2). CD63 expression or CD203c upregulation on basophil surface have been reported as new diagnostic markers for allergic diseases (Figure 3). In several studies the BAT based on the occurence of CD63 (gp53) in the presence of allergen was found sensitive (80-100%) and specific (100%) for the *in vitro* diagnosis of pollen allergy. The expression of CD63 has a good correlation with basophil degranulation and histamine release. Using grass pollen or mite (*Dermatophagoides pteronyssinus*) allergens, IgE-dependent activation of basophils is associated with upregulation of basophil surface markers. Measurement of CD203c upregulation on basophils in response to specific allergens as a specific basophil activation marker has been shown to be a reliable and effective *in vitro* diagnostic test as CD63 expression.

BATs are considered to identify difficult IgE-mediated allergic cases especially when patient history, skin tests or specific IgE results are discordant. In contrast to skin testing, CD203c-based BAT can be performed in patients without wash-out for antiallergic treatment.

BAT is found to be more sensitive than detection of nasal specific IgE and less time consuming compared to nasal provocation tests in



Secreted mediators	Methods of measurement
Granules example: histamine	Fluorimetry
Lipids example: LTC4	RIA/ELISA
Cytokines example: IL-4	ELISA

Figure 1 Measurement methods of secreted mediators after the basophil activation by allergens. *(Modified from Ebo DG, Saninte-Laudy J, Bridts CH, et al. Flow-assisted allergy diagnosis: current applications and future perspectives. Allergy 2006;61:1028-1039 and MacGlashan DW Jr. Basophil activation testing. J Allergy Clin Immunol 2013;132:777-787.)*

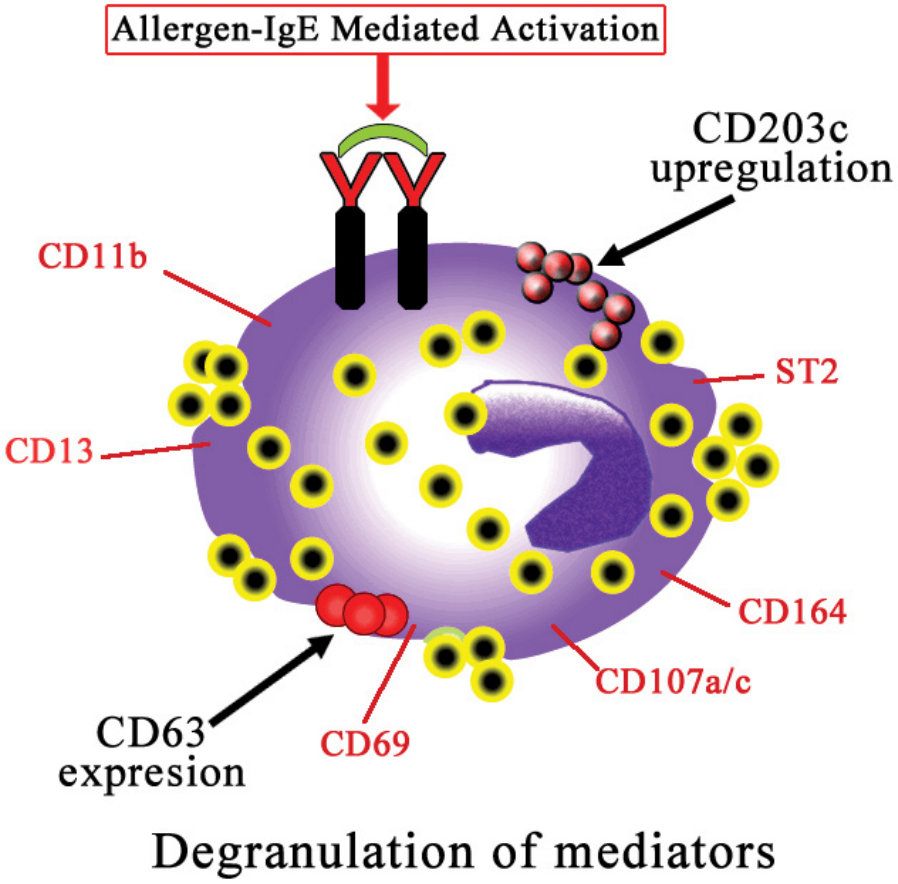


Figure 2 Identification of increased or newly expressed basophil surface proteins by using polychromatic flow cytometry. *(Modified from Ebo DG, Saninte-Laudy J, Bridts CH, et al. Flow-assisted allergy diagnosis: current applications and future perspectives. Allergy 2006;61:1028-1039 and MacGlashan DW Jr. Basophil activation testing. J Allergy Clin Immunol 2013;132:777-787.)*

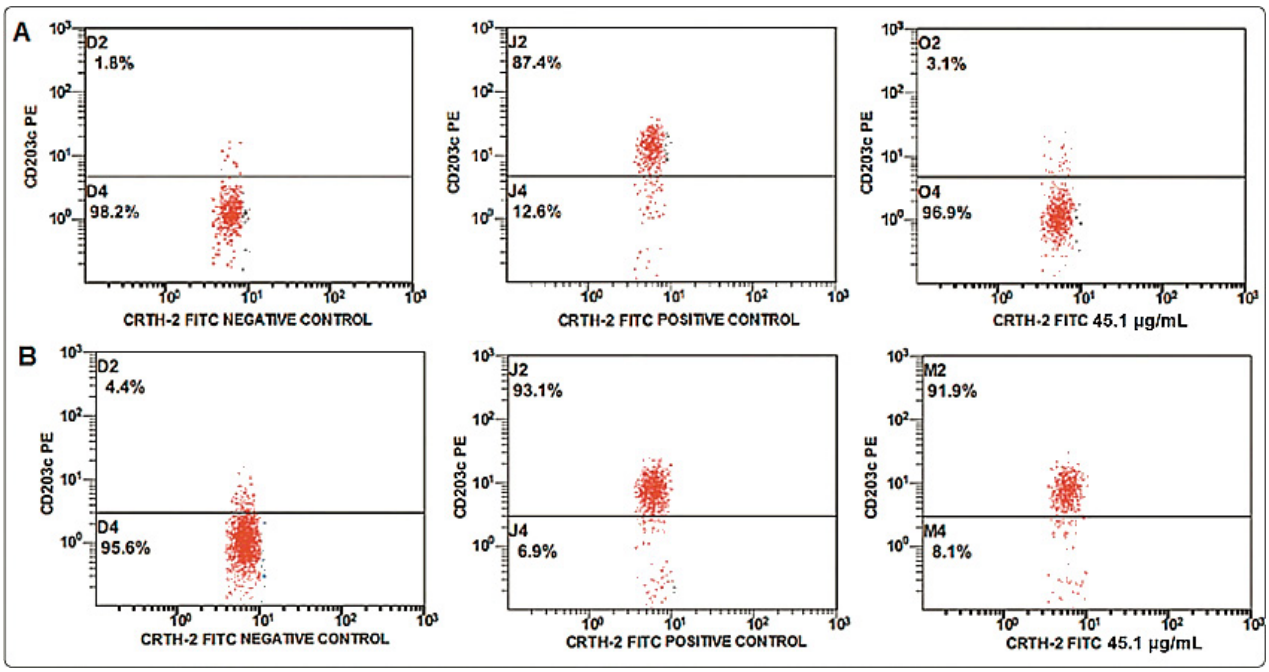


Figure 3 Flow cytometric detection in healthy control (A) and a patient with seasonal allergic rhinitis (B) ; Representative increased expression of CD203c on the basophil surface by pollen allergen stimulaton. A1, B1 ; negative control, A2, B2 ; positive control, A3, B3; stimulation with 45,1 µg/ml of *pheleum pratensis* concentration. *(Modified from Özdemir SK, Güloglu D, Sin BA, Elhan H, İkincioglları A, Misirligil Z. Reliability of basophil activation test using CD203c expression in diagnosis of polen allergy. Am J Rhinol Allergy 2011;25:e225-e231.)*

local AR. The use of higher doses of allergen stimulation may be required because of low amounts of specific IgE in these cases.

Recently, it has been suggested that increased CD63 expression or CD203c upregulation might be useful tools for early monitoring of the development of protective immune response induced by AIT.

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9 NEW DIAGNOSTIC AND RESEARCH TECHNIQUES IN ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- 'Omic' technologies represent a front technique for research focus on the universal detection of genes (genomics), mRNA (transcriptomics), DNA methylation, histone modifications or non-coding RNA (epigenetics), proteins (proteomics), lipids (lipidomics) and small molecule metabolites (metabolomics) in a specific biological sample
- 'Omic' experiment is hypothesis-free; generates unbiased results by an extensive bioinformatic analysis and should be validated in the functional experiments
- Next Generation Sequencing (NGS) is a high-throughput, multiplexed sequencing method, which is used in genomics, transcriptomics and epigenetics, while mass spectrometry is used for detection of analytes in proteomic, lipidomic and metabolomic research
- International evidence-based guidelines help patients and clinicians in allergic rhinitis and chronic rhinosinusitis diagnosis and management
- Omics technologies do not have a place in routine diagnosis so far

We are witnessing the fast acceleration of research technologies, including 'omic' and others, which are currently being implemented in the studies on allergic rhinitis (AR) and chronic rhinosinusitis (CRS) pathogenesis, diagnosis and management (Figure 1). Several of these techniques will soon develop into the standard clinical tools. 'Omic' technologies and their integration are referred as systems biology. These experiments differ from traditional studies, which are largely focused around a hypothesis. By contrast, the goal of an 'omic' experiment is to create an hypothesis-free, holistic view of the molecules involved in the functional and/or structural alterations within the cells and tissues. In such an experiment, all data are simultaneously acquired and analyzed to further define a specific hypothesis for testing. Together with the progress in the primary cell culture techniques, combined with the molecular biology and cell imaging tools, 'omic' techniques are becoming crucial in understanding etiology of the disease, screening, diagnosis and prognosis (so-called biomarkers discovery) (Figure 2). Moreover, they are increasingly being used in drug discovery and assessment of their toxicity and efficacy. Most of these technologies are being developed into high-throughput and multiplexed assays, which significantly lower the costs and decrease time to obtain the enormous amount of data. Because of that, in parallel with the 'omic' technology, there is a fast improvement in the data analysis and bioinformatic tools to comprehend and understand the results.

Genomics was the first 'omic' technologies to be developed, which progressed beyond DNA sequencing (structural genomics) to identifying the function of the encoded genes (functional genomics). Genomics has been focused on detecting structural variations in the coding and non-coding parts of DNA such as single nucleotide polymorphisms (SNPs) in different tissues and their associations with

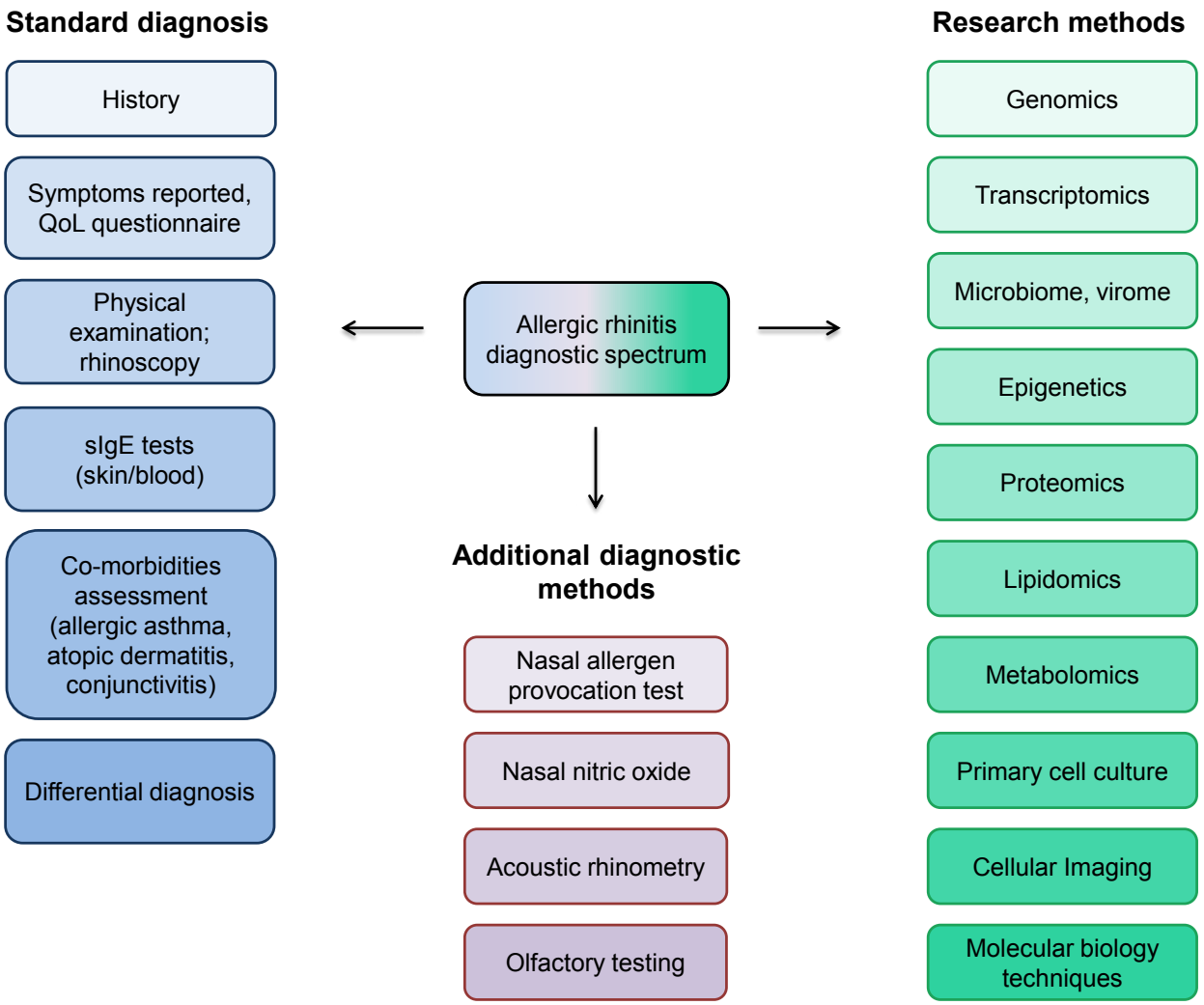

Figure 1 Current, novel diagnostic and research methods in allergic rhinitis.

the disease occurrence or with the different response to treatment (pharmacogenomics). Genomics is currently frequently used in the studies, identifying DNA of microorganisms that are inhibiting human body, which are referred as microbiome. Nasal mucosa is one of the tissues in which interaction between the microbiome and the host might shape the mucosal barrier function and response to allergens and irritants. With the progress of the genomics a global concept developed, suggesting that not only the DNA/gene structure, but the gene expression might reflect the functional state of the organisms. Transcriptomics is the study of the total mRNA, reflecting the genes that are actively expressed at any given moment. Since viral infections of the nose are extremely popular, they might also modulate the AR and other diseases of the nose and connected organs. Therefore, it is increasingly more common to identify viral strains invading the nasal mucosa by genomic and transcriptomic methods. Epigenetic changes reflecting the influence of the environment on the nasal mucosa and leading to the non-genetic changes of chromatin or DNA are also currently studied by means of 'omic' technologies. Chromatin changes, histone modifications are studied by DNAse-seq and ChIP-seq, while DNA methylation and non-coding RNA expression (miRNA, lncRNA, etc.) are studied by sequencing. Most of these 'omic' technologies described above have been developed on

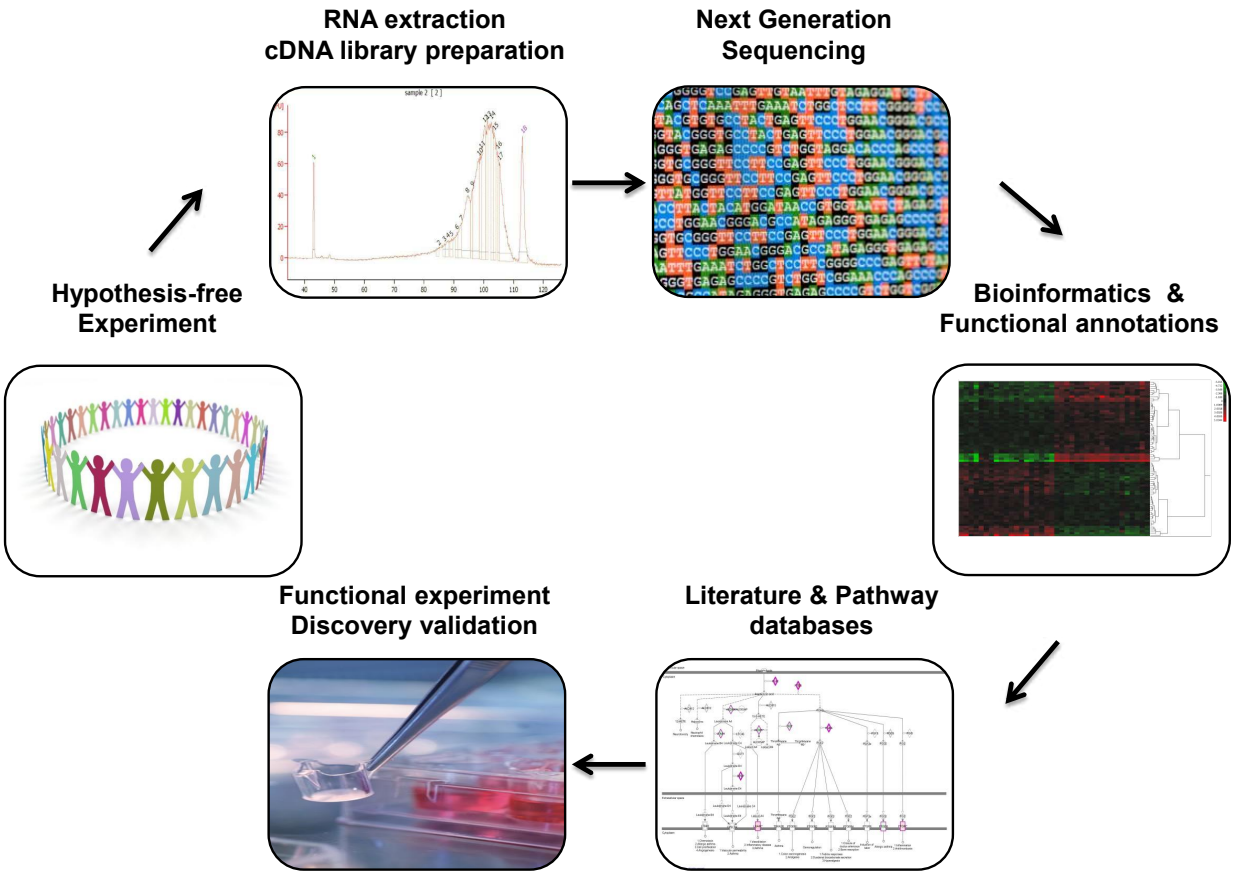

Figure 2 Transcriptomics experiment sequential flow-chart.

the basis of DNA or RNA microarray chips and are currently being accessible on the platform of high-throughput and multiplexing technique called next-generation sequencing. Proteomics and lipidomics are large-scale studies of proteins or lipids, respectively, including their structure, functions, pathways and networks within the cell, tissue and organism. In nasal settings, proteomics and lipidomics focus on cells of mucosal lining, as well as on the secretome of nasal fluid. Proteomics and lipidomics hold special promise in the AR biomarker discovery, as the local nasal allergic inflammation reflects full spectrum of the disease, biomarker are likely to occur here in higher concentrations than in the blood, and the nose is easily accessible. Metabolomics is a study of global low molecular weight compounds (metabolites) present in a cell or organism that participate in metabolic reactions. The metabolome contains many different biological molecules which are physically and chemically very complex. Proteomics, lipidomics and metabolomics require sample fractionation by e.g. chromatography and further analysis by using a mass spectrometry. Finally, hypothesis generated due to the 'omic' technology and bioinformatic processing can be now tested experimentally due to the advancement of primary nasal epithelial cell and sinus cell culture techniques, such as air-liquid interphase cultures. International evidence-based guidelines help patients and clinicians in allergic

TABLE 1

Current diagnostic procedures in allergic rhinitis
Standard diagnosis in AR should include all of the following points:
a. History and quality of life assessment
b. Nasal symptoms reported (sneezing, rhinorrhea, itching of nose, eyes, palate; postnatal drip, frequent throat clearing, cough, malaise or fatigue (esp. in children)
c. Physical examination including anterior rhinoscopy (clear rhinorrhea, bluish or pale swelling of nasal mucosa, ocular findings e.g. watery discharge, swollen conjunctivae, scleral injection; allergic shiners, nasal crease, frequent throat clearing; absence of foreign body, tumor, purulence suggesting infection)
d. sIgE (skin or blood tests)
e. Common co-morbidities diagnostic approach (atopic dermatitis, allergic asthma, otitis media, conjunctivitis; possibility of coexistence of allergic and non-allergic causes of rhinitis)
f. Differential diagnosis (vasomotor rhinitis, non-allergic chronic rhinosinusitis, infections, hormonal drug-related, occupational rhinitis; CSF rhinorrhea, tumors, nasal polyps)
Additional diagnostic tools, not used as standard methods
a. Nasal allergen provocation test
b. Nasal nitric oxide
c. Acoustic rhinometry
d. Olfactory testing

rhinitis and chronic rhinosinusitis diagnosis and management (Table 1). Omics technologies do not have a place in routine diagnosis so far.

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10 MEASURING ALLERGEN EXPOSURE

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KEY MESSAGES

- All pollen tested so far varied >10-fold in their daily amount of major allergen released per pollen (pollen potency)
- Pollen allergen release potency is not geographical fixed and changes between years
- Pollen allergen release potency is probably determined in the week before pollination by two simultaneous competing ripening processes: anther development governing pollen emission and individual pollen ripening determining the allergen content of pollen
- Measuring exposure by determining the evoking factor on a molecular level (molecular aerobiology) will provide a more reliable measure of exposure

Allergy against pollen is the most frequent allergic airway disease. The prevalence of grass pollen sensitizations has surpassed house dust mite sensitizations, and if sensitizations to birch and other pollen are added, allergy against pollen is clearly the number one allergic airway disease. It is therefore no surprise that monitoring pollen is the only voluntarily performed air quality monitoring in Europe, whereas air quality monitoring of PM10, carbon black, NO2 and O3 are governmental funded activities to reduce man-made pollution. Measuring pollen is a major endeavor as many sites need to be monitored daily and manually, and no satisfactory automated pollen monitors are functionally available. Currently, a network of about 350 pollen monitoring stations is spread over Europe.

Monitoring pollen is a good predictor of allergy symptoms. However, the human immune system does not react to the pollen but to substances released by pollen, the most important ones being the allergens. Most pollen release a major allergen like Bet v 1 from birch pollen or Ole e 1 from olive pollen.

Monitoring airborne allergens instead of airborne pollen is tedious and not frequently done. However, in all cases reported pollen counts varied widely in their major allergen release per pollen i.e. in their allergen release potency. In Figure 1 the release of Ole e 1 from olive pollen in Portugal is displayed. At the end of the olive pollen season a low number of airborne olive pollen was counted, but the major olive pollen allergen Ole e 1 was highest of the whole season. Thus pollen counts may underestimate allergen exposure. In Figure 2 a similar story is told for birch pollen: both airborne Bet v 1 and birch pollen were monitored. Expected was that the pollen potency, i.e. the amount of Bet v 1 calculated per pollen, would be constant. Thus the curve for pollen potency should be a straight line parallel to the x-axis. This was however seldom the case in Europe and only during brief periods. In Figure 2A only the example of Munich in Germany is shown. Calculating the origin of the pollen revealed that pollen with a deviating potency stemmed from different regions. In general however, already the same pollen from the same region vary up to 10-fold in their potency to release the major allergen (Figure 2B). Unpublished observations showed that the same holds true for grass pollen.

In older investigations house dust mite exposure was measured by counting the number of house

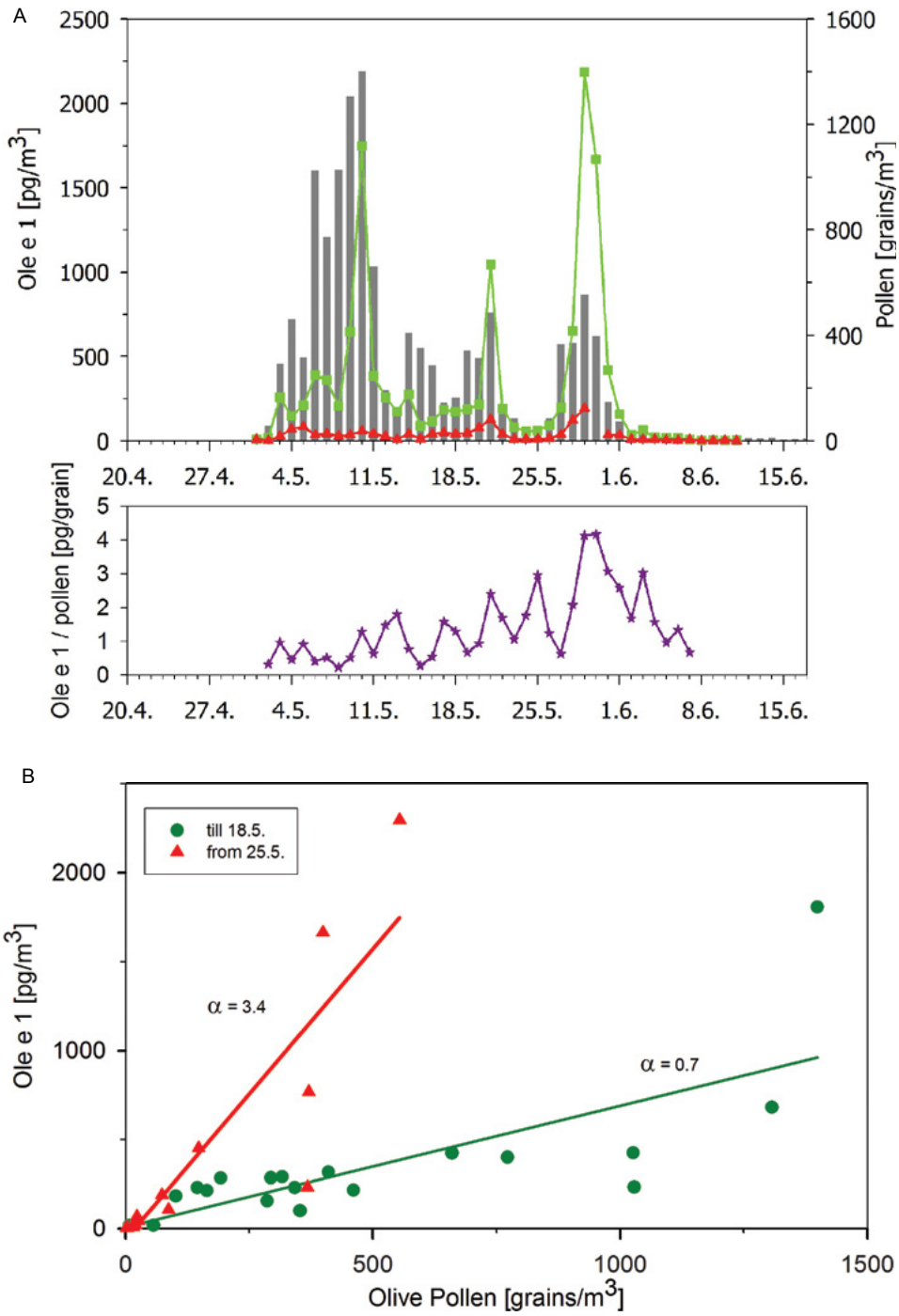

Figure 1 (A) Concomitant monitoring of airborne olive pollen and major olive pollen allergen Ole e 1. At the end of the season when pollen counts (grey bars) were low, high Ole e 1 levels (green curve is Ole e 1 in PM>10µm, the red curve is Ole e 1 in 10µm>PM>2.5µm) were detected. (B) Pollen counts versus airborne Ole e 1. The slope (α) of the curve represents pollen potency. The pollen potency was much higher at the end of the pollen season in Evora, Portugal, 2009. (*Reproduced with permission from Galan C, Antunes C, Brandao R, et al. Airborne olive pollen counts are not representative of exposure to the major olive allergen Ole e 1. Allergy, 2013;68:809-812, with permission from Willey Blackwell.*)

dust mite per surface area. Nowadays exposure is determined by measuring the amount of house dust mite allergen Der p 1, Der p 2, Der f 1 and Der f 2 per surface area instead. We now can do the same for pollen.

From the above examples we can deduce that probably any allergen from natural sources has a variability in releasing major (and probably also minor) allergens. As most allergens are natural products, we expect this to hold true for all allergens. Thus, measuring exposure by determining the evoking factor on a molecular level (molecular aerobiology) should have advantages. Until that is established, the measuring of airborne whole pollen grains remains a good alternative.

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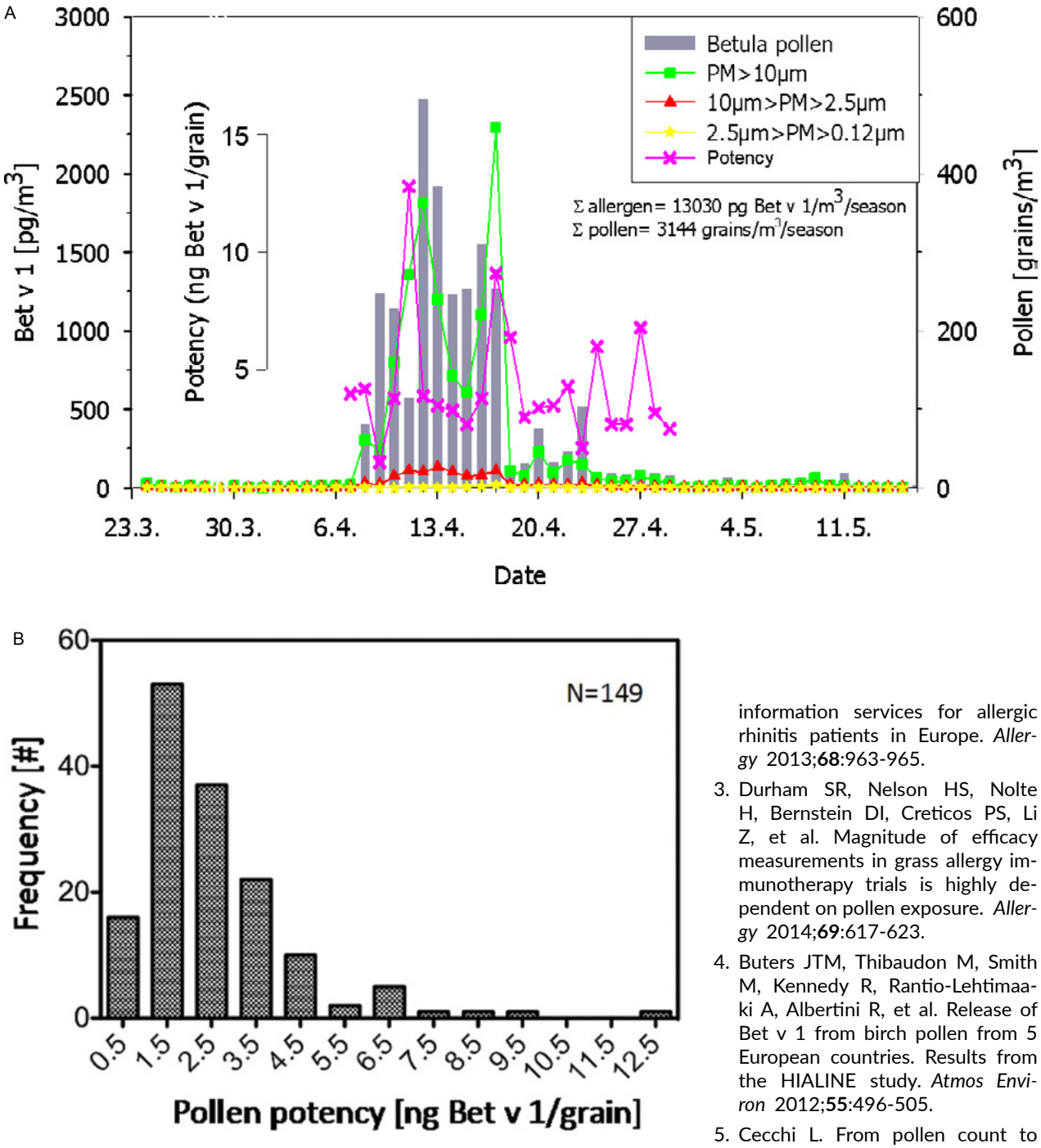

Figure 2 (A) Birch pollen flight (grey bars) and airborne birch allergen Bet v 1 (the pink curve is allergen per pollen grain i.e. potency) in Munich, Germany 2009. (B) Histogram of pollen potency (allergen release per pollen) for Munich, Germany in the years 2007-2011. The same amount of pollen may release over 10-fold different amounts of Bet v 1. (*From Buters JTM, Thibaudon M, Smith M, Kennedy R, Rantio-Lehtimaaki A, Albertini R, et al. Release of Bet v 1 from birch pollen from 5 European countries. Results from the HIALINE study. Atmos Environ 2012;55:496-505.*)

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11 DIAGNOSIS OF ALLERGIC RHINITIS-MEASURING HEALTH-RELATED QUALITY OF LIFE

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KEY MESSAGES

- Health-related quality of life (HRQOL) instruments were introduced because clinical symptoms correlate only moderately with patient perceptions
- To evaluate HRQOL in allergic rhinitis (AR), generic and specific questionnaires have been validated
- HRQOL questionnaires in AR are useful in clinical trials, in epidemiological studies and in clinical practice
- AR have a significant impact on HRQOL in comparison with healthy subjects or even in comparison with other diseases such as asthma

Health-related quality of life (HRQOL) is usually defined as a multidimensional concept encompassing the physical, mental, and social components associated with an illness or its treatment.

The reason to introduce HRQOL instruments in clinical practice or in clinical research is that the personal burden of any illness, as perceived by the patient, cannot be fully assessed by traditional clinical symptoms and signs since they are correlating only moderately with patient perceptions and functional capabilities on a daily basis. The importance of HRQOL in allergic rhinitis (AR) is demonstrated by the fact that in the last years the term AR and quality of life appeared cited in Pubmed more than 1,500 times.

Both generic and disease-specific instruments have been used to evaluate the impact of AR and its treatment on patients' HRQOL. Such instruments are useful for assessing treatment efficacy in clinical trials, for measuring the burden of disease in epidemiological studies, or as monitoring tool in clinical practice. Both generic and disease specific tools are useful, but their properties must be kept in mind. Generic instruments (Table 1) have the advantage of comparing unrelated diseases but are less sensitive to detect the burden of the disease. They are based on general health issues and include items on physical activity, physiologic status, capability of self-care, level of pain/stress and social integration. Generic instruments are also useful to compare cost-efficacy interventions. Disease specific questionnaires (Table 2) are more sensitive to changes and focus on items related to the disease, without the possibility to allow comparison between diseases. In the 90´s, several authors, using generic questionnaires, demonstrated that AR has a significant impact on HRQOL in comparison with healthy subjects (Figure 1)

TABLE 1

Generic instruments measuring the Health-related quality of life
• MOS SF-36/12 Generic health-related quality of life measure
• SAT-P Daily life satisfaction profile
• Profile of Mood States (POMS)
• VAS Appraisal of General Health
• VAS-QoL
• Munich Life Dimension List
• The Nottingham Health Profile
• The Sickness Impact Profile
• The EQ-5D
• 15-dimensional instrument for measuring HRQL (15D)

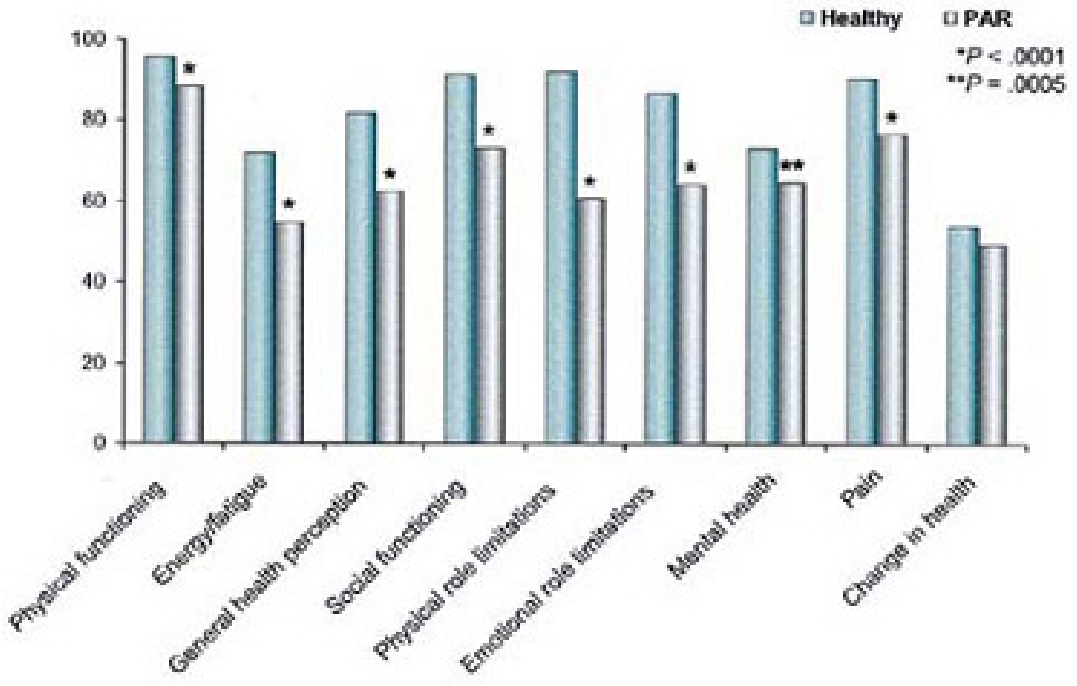

Figure 2 QOL scores in adults with perennial allergic rhinitis and healthy control subjects. (*Data from Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol. 1994;94:182-188.*)

TABLE 2

Disease specific questionnaires for Health-related quality of life in:
A. Allergic rhinitis
RQLQ - Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S) - Standardised Rhinoconjunctivitis Quality of Life Questionnaire
MiniRQLQ - Mini Rhinoconjunctivitis Quality of Life Questionnaire
RhinQLQ - Rhinitis Quality of Life Questionnaire
AdolRQLQ - Adolescent Rhinoconjunctivitis Quality of Life Questionnaire
PRQLQ - Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
Perceived control of rhinitis questionnaire
RSDI - Rhinosinusitis Disability Index
ESPRINT 28 & ESPRINT 15
B. Allergic rhinitis and other diseases
PADQLQ - Pediatric Allergic Disease Quality of Life Questionnaire
Rhiniasthma Quality of Life Questionnaire for patients with asthma and rhinitis
PAR-ENT to assess the impact of children's recurrent otolaryngologic infections on their parents' QOL

TABLE 3

Main Characteristics of two Health-related quality of life questionnaires in used in allergic rinitis (ESPRINT-15 and the MiniRQLQ)

	Number of items	Number of dimensions	Dimensions	Overall and dimension scores	Score ranges
MiniRQLQ	14	5	Activity limitations Practical problems Nose symptoms Eye symptoms Other symptoms	Yes	Overall and dimension scores from 0 (no impairment) to 6 (greatest impairment)
ESPRINT-15	15	4	Symptoms Daily activities Sleep Psychological impact	Yes	Overall score from 0 (minimum impact in HRQOL) to 5.8 (maximum impact in HRQOL) Dimension scores from 0 (minimum impact in HRQOL) to 6 (maximum impact in HRQOL)

(Reproduced with permission from Valero A, Alonso J, Antépara I,, et al. Health-related quality of life in allergic rhinitis: comparing the short form ESPRINT-15 and MiniRQLQ questionnaires. Allergy, 2007;62:1372-1378, with permission from Willey Blackwell.)

or even compared with other diseases such as asthma. Also in the 90´s the first questionnaires specific for AR were developed.

Any questionnaire of HRQOL measurement requires meeting some psychometric characteristics before it can be used in clinical practice. The validation of the questionnaires must evaluate its' feasibility (ease to use), reliability (internal consistency), validity (good correlation with symptoms related to the disease and with other questionnaires), the floor and ceiling effects (the proportion of patients with the worst and best possible scores), sensitivity to change (the size effect) and the minimal important difference. Other characteristic that must keep into consideration is the cultural adaptation since each questionnaire must be adapted and validated for use in different cultures and/or countries and for different age groups of patients.

HRQOL questionnaires in AR include dimensions (or domains) related to the disease such as nasal and non-nasal symptoms, activities of daily life, practical problems, energy/vitality, environmental aspects, sleep problems and mood. In general, they include around 25 to 30 domains, but some questionnaires have the so call "short version" including 12 to 15 domains (Table 3).

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12 BIOTECHNOLOGY FOR THE DIAGNOSIS OF ALLERGIC RHINITIS

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KEY MESSAGES

- Biotechnology has experienced spectacular advances over the last decades that have significantly contributed to improve diagnosis of allergic diseases
- The identification of the clinically relevant allergenic molecules is nowadays possible by combining biotechnological procedures (i.e. phage display, proteomic tools, mass spectrometry, etc.) with bioinformatics and databases
- The availability of well-defined purified allergens produced as recombinant proteins or directly obtained from the allergenic sources, has facilitated the implementation of the allergen-based concept of component-resolved diagnosis (CRD)
- Biotechnology contributed to the elucidation of individual sensitization patterns and the identification of patients suffering from local allergic rhinitis (AR) without systemic atopy, which constitute major goals achieved in diagnosis of AR

"Biotechnology is the use of living systems and organisms to develop or make useful products, or any technological application that uses biological systems, living organisms or derivatives thereof, to make or modify products or processes for specific use" (UN Convention on Biological Diversity, Art. 2). Biotechnology and the diagnosis of allergic rhinitis (AR) are closely linked via the most prominent clinical parameter in AR, specific IgE (sIgE) Specific IgE and thus the allergen sensitization profile of the patient is the key parameter for the diagnosis of AR and allergic diseases in general. The first read-out in daily practice is a positive skin-prick test for aeroallergens, followed by in depth determination of the sensitization pattern in terms of sIgE in serum, locally in nasal biopsies, or bound on effector cells. A high sensitivity, specificity, reproducibility and thus a high reliability of diagnostic tests for sIgE depends on the identification and availability of the relevant allergens.

The most straightforward approach is the collection of the allergenic sources, or parts of it, or the cultivation of the allergenic organisms to subsequently extract the allergenic molecules for diagnostic purposes. These already constitutes by definition biotechnological processes. The main pitfalls here encompasses the notorious difficulties in standardization of extracts and the possible under representation of important allergenic molecules in them, which might lead to false positive and negative results, thus hampering proper diagnosis of AR.

The incredible progress experienced by biotechnology over the last decades has significantly contributed to overcome some of these problems. First of all, biotechnological processes such as phage surface display of complementary DNA libraries, selections by yeast two hybrid systems or the use of proteomics tools together with bioinformatics and databases have significantly improved the identification of relevant allergens (Figure 1). These identified molecules, usually proteins, are generated and/or modified using molecular biology techniques like polymerase-chain reaction (PCR), site directed mutagenesis or *de novo* gene synthesis and used to clone and express large amounts

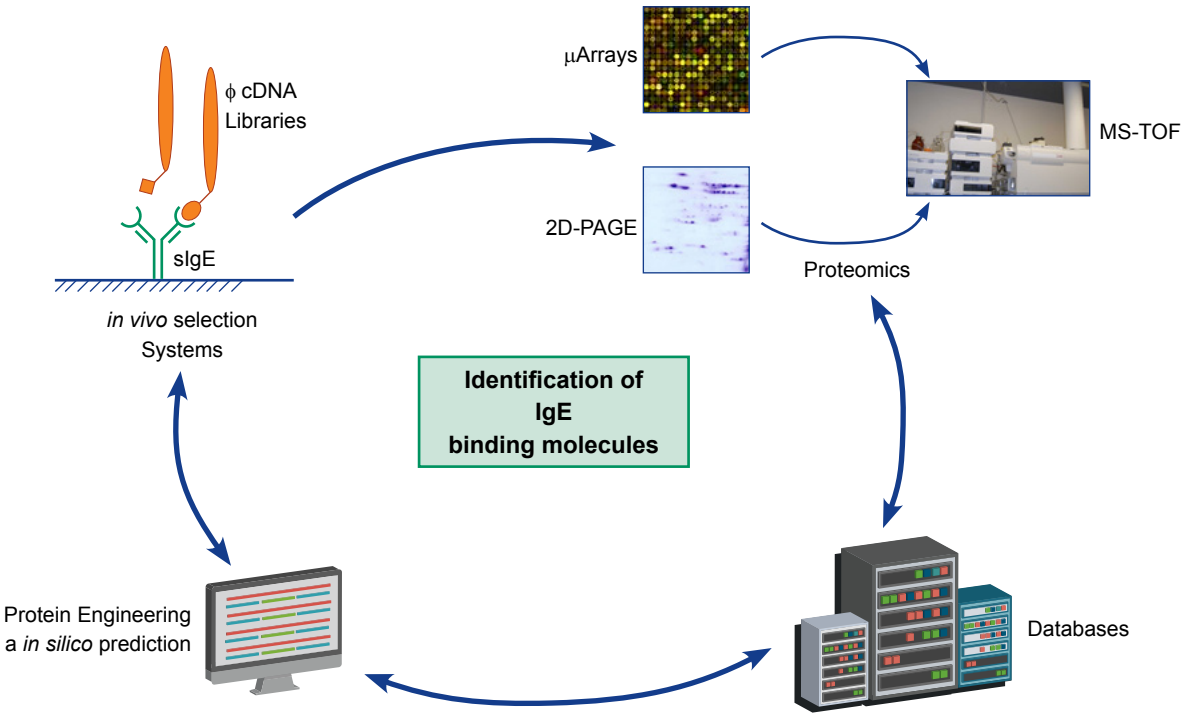

Figure 1 Different methodologies can be used for the identification of IgE binding molecules, either isolated or in iterative interplay. Technologies like the display of cDNA libraries derived from allergenic organisms on the surface of bacteriophage and selection of binders on immobilized IgE from allergic patients led to identification of a plethora of novel allergens. Recent progress in the resolution of mass spectrometry facilitated the identification of IgE binding proteins. This approach is strongly depended on the availability of large protein databases. In addition, *in silico* discovery of allergens by rational examination of structures and primary sequences by expert systems and pattern recognition facilitated the discovery of novel allergens.

of allergens in heterologous hosts and to purify them to homogeneity using chromatographic and/or other biochemical methods and techniques. Alternatively, if these allergens are contained in sufficient amount, they can also be directly purified to homogeneity from the allergenic source (Figure 2).

The endpoint of this process is the availability of well characterized diagnostic agents fulfilling the needs of clinical practice to diagnose and distinguish AR from NAR, as well as the relevant regulations for the diagnostic industry (e.g ISO 13485, 23640). The use of purified natural and recombinant allergens for the diagnosis of AR has established the new allergen-based concept of component resolved diagnosis (CRD). The CRD together with the other above described advances in biotechnology has certainly contributed to improve the diagnosis of AR, for example, with the identification of patients with local allergic rhinitis suffering from local nasal allergic responses without systemic atopy.

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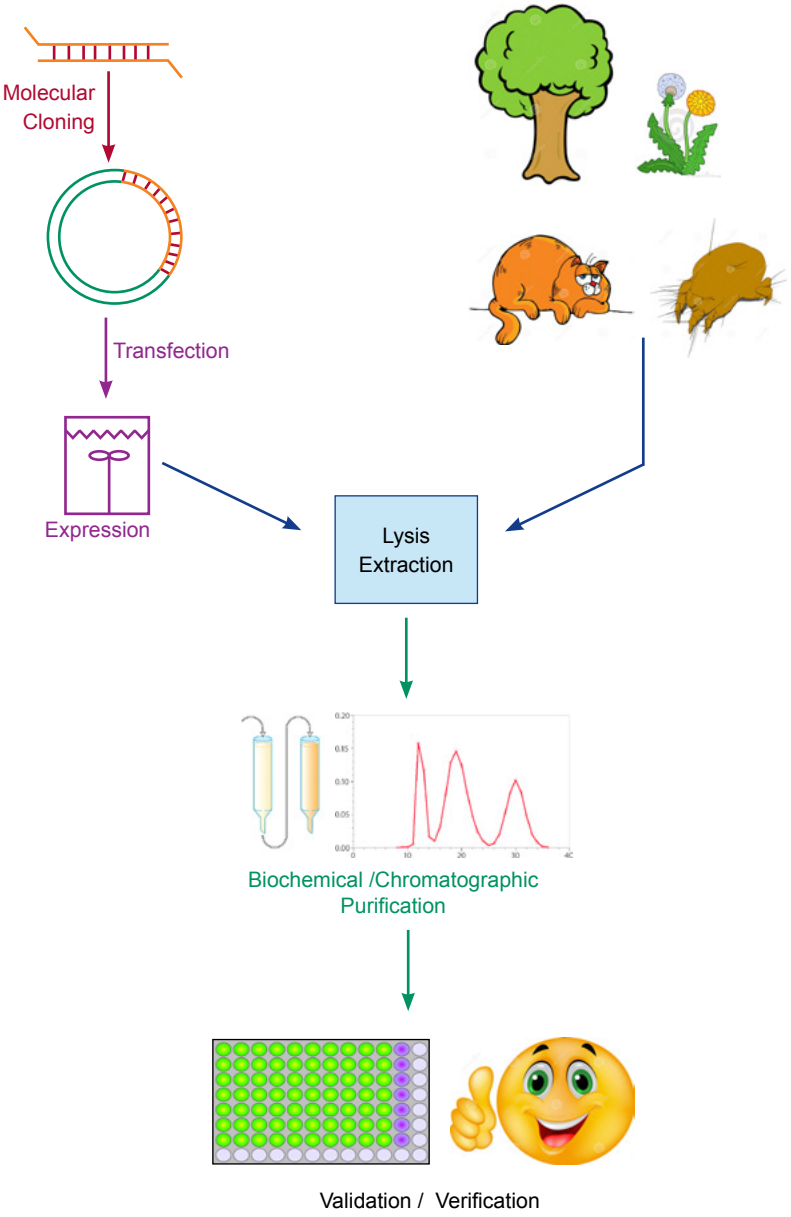
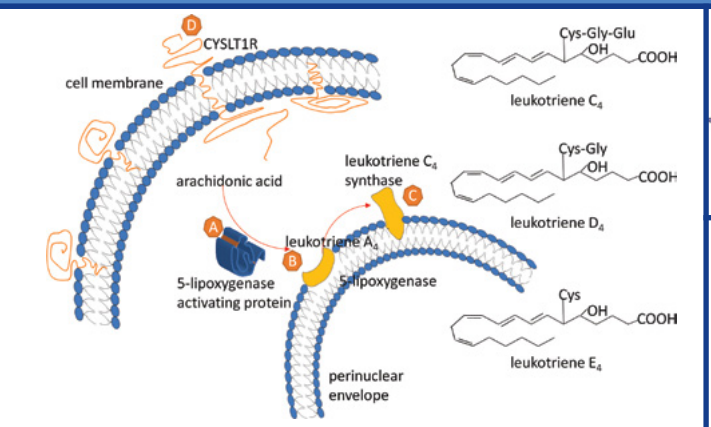
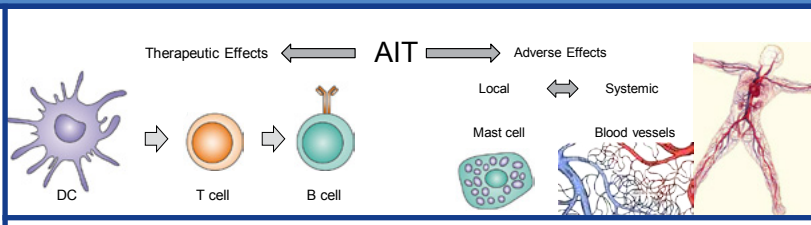
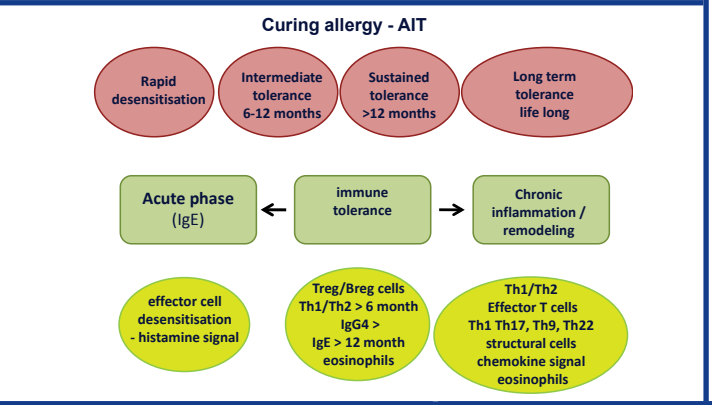


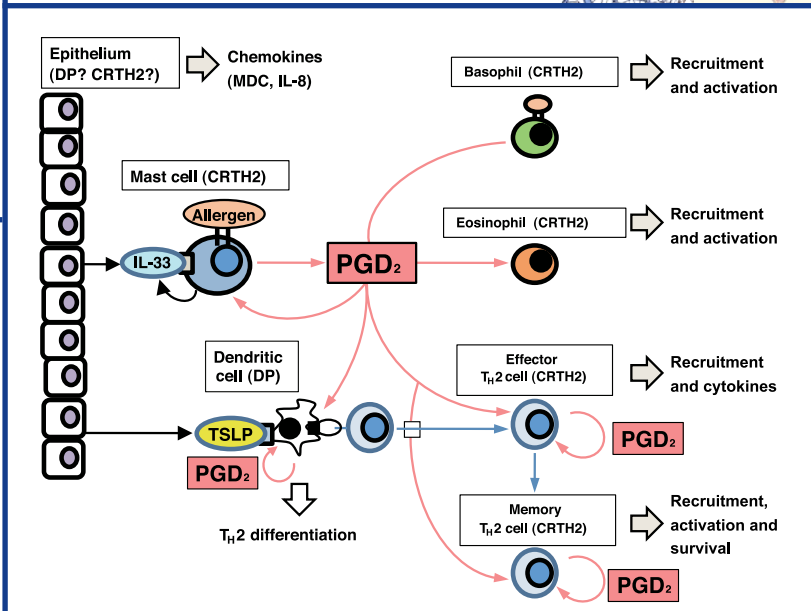
Figure 2 The production of pure allergens is mainly pursued by two approaches: a) the coding sequence of the allergen is amplified by PCR, cloned in a suitable vector for expression in heterologous hosts and sometimes supplemented with a polypeptide tag for purification. Commonly used hosts for the production include e.g. *Escherichia coli*, *Pichia pastoris* and mammalian cell lines. Allergens from natural sources are collected either from the whole organism or dedicated parts of it e.g. pollen or fruits. In both cases the proteins of interest are extracted with biochemical methods and purified using chromatography (affinity, SEC, IEX etc.). A very important aspect after the preparation of allergens or allergen extracts is the verification and determination of the biological relevance by serology and/or *in vivo* tests.

Section E









ALLERGIC RHINITIS - TREATMENT

* Treatment of allergic rhinitis - overview
* Management of allergic rhinitis – allergen avoidance
* Antihistamines in the treatment of allergic rhinitis
* Treatment of allergic rhinitis – nasal steroids
* Antileukotrienes in the treatment of allergic rhinitis
* Additional drug treatment options for allergic rhinitis
* Conservative non-drug treatment for allergic rhinitis
* Allergen immunotherapy for allergic rhinitis - overview
* Subcutaneous allergen immunotherapy for allergic rhinitis
* Sublingual immunotherapy for allergic rhinitis
* New vaccines for allergen immunotherapy
* AIT for allergic rhinitis - new delivery options
* Regulation and standardization of AIT extracts
* Treatment of allergic rhinitis with biologicals and monoclonal antibodies
* Other targeted treatment options for allergic rhinitis
* Pharmacogenetics of allergic rhinitis
* Complementary and alternative medicine for allergic rhinitis

1 TREATMENT OF ALLERGIC RHINITIS - OVERVIEW

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KEY MESSAGES

- Ideally, allergic rhinitis (AR) treatment should restore and enable the patient to achieve normal social function, olfaction, taste, and restful and peaceful sleep
- Controlling AR is of paramount importance for quality of life issues and to decrease the severity of co-morbidities associated with AR
- The rationale and methods to treat AR are much the same today as they were 40 to 50 years ago, however, today, treatment is more scientifically based and effective and associated with less side effects
- Elimination of an offending allergen from a patient's environment is an effective method to control symptoms of AR
- Second generation antihistamines are not only effective to control the symptoms of AR, but are mostly devoid of major side effects. Topical (intranasal) glucocorticosteroids are perhaps one of the most effective modes of therapy since they control nasal congestion, one of the most difficult symptoms associated with AR to resolve
- Properly prescribed subcutaneous or sublingual allergen immunotherapy (AIT) is another cost -effective treatment for AR

Ambient air, as it enters the nose, whatever its temperature and humidity, is warmed and humidified almost to body temperature by the time it reaches the laryngopharynx. Likewise, a normal anatomy and intact and normally functioning mucosal and mucocilliary transport system results in filtration of most particles greater than 4.5 microns. Allergic rhinitis (AR) disrupts the normal function of the upper airway causing considerable disability, comorbidities, and loss of quality-of-life (QoL).

GOALS OF TREATMENT

The primary goal of a physician or other healthcare professional diagnosing and treating any upper airway disease is to restore normal function to the upper airway. To do so, an understanding of normal anatomy, physiology, local and systemic defense systems, and various diseases which affect the upper airway (Figure 1) is of paramount importance. For example, nasal obstruction not only occurs from nasal mucosal edema associated with AR, but also, to mention a few, from a severely deviated nasal septum, nasal polyposis (NP), various medications and large adenoids and tonsils. Likewise, other symptoms of AR such as sneezing, itching, and rhinorrhea can be associated with a variety of different upper airway diseases, such as laryngopharyngeal esophageal reflux disease, non-allergic rhinitis, and acute and chronic rhinosinusitis.

Thus, restoring normal nasal physiologic function, in other words patency of the upper airway and resolution of excessive rhinorrhea and irritation of the nose manifested by sneezing and nasal pruritus is the primary goal of treating AR. Ideally, AR treatment should restore and enable the patient to achieve normal social function, olfaction, taste, and restful and peaceful sleep.

Controlling AR is of paramount importance for QoL issues and to decrease the severity of co-morbidities associated with AR. A decreased QoL associated with AR is often greater than with many

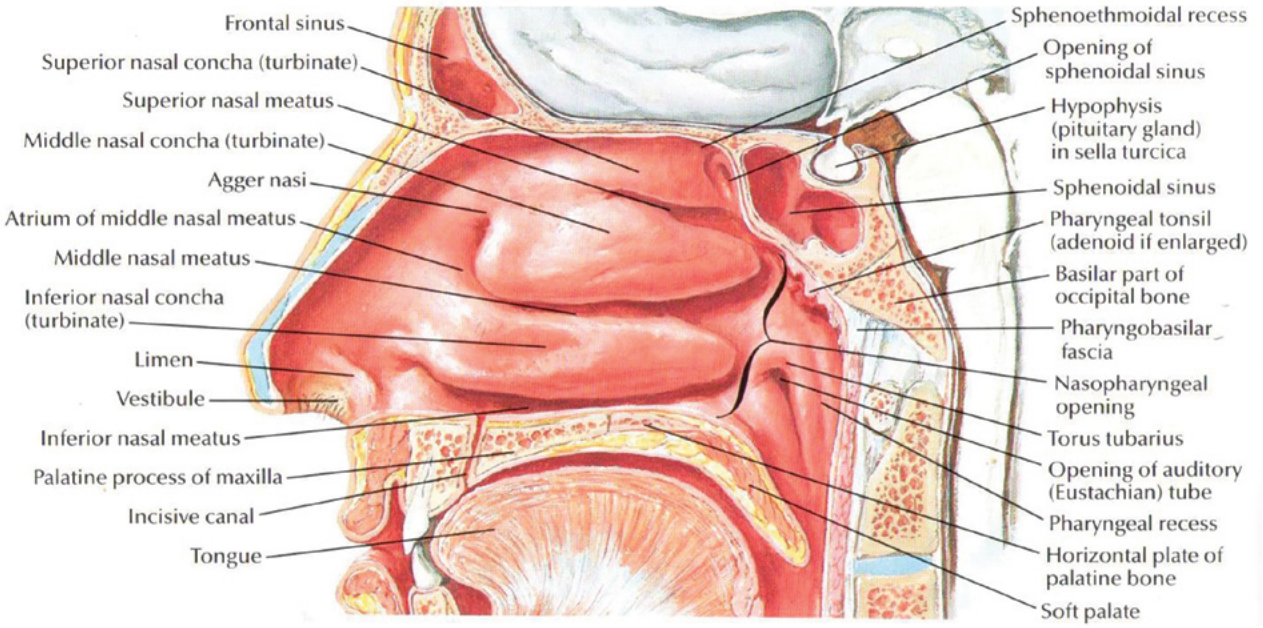


Figure 1 The complexity of the upper airways – the lateral nasal wall.

other diseases, including asthma. This is not only because of the symptoms primarily associated with AR rhinitis but also because of associated symptoms such as post-nasal drip, red, itchy, watery eyes, headaches, facial discomfort, and ear discomfort (Figure 2). Mostly, AR patients feel tired, irritable, and sometimes depressed, not to mention the fact that they are often embarrassed because of symptoms associated with their malfunctioning upper airway (Figure 3). Co-morbidities of AR include asthma, atopic dermatitis (AD), allergic conjunctivitis, acute rhinosinusitis, chronic rhinosinusitis with/without nasal polyps, frequent upper respiratory tract infections, otitis media and others. Secondary problems can result, for example sleep disorders, learning disabilities, and dental malocclusion (Table 1). In addition the financial burden is a considerable problem as measured by the direct and indirect costs derived from absenteeism from work and school, as well as from decreased productivity.

RATIONALE AND METHODS TO TREAT

Treatment of AR is more scientifically based and effective than it has been in the past.

For example, elimination of an offending allergen from a patient's environment always has been an effective method to control symptoms of AR. However, today, there is a better rationale and more knowledge about how to eliminate one allergen versus another and the time it takes to do so. It is now recognized that different dust mites affect different geographic populations throughout the world and that it takes up to five to six months to eliminate pet dander from the home. Cockroach allergens may affect those who live in the inner city.

Second generation antihistamines are not more effective to control the symptoms of AR than first generation antihistamines, but they are

TABLE 1

Comorbidities of Allergic Rhinitis

Primary	Secondary
Allergic asthma	
Atopic dermatitis	Sleep deprivation
Allergic conjunctivitis	Social dysfunction
Acute and chronic sinusitis	Decreased productivity
Nasal polyps (rare)	Absenteeism
Increased upper respiratory tract viral infections	Increased fatigability
Otitis media	Learning impairment
Food allergy	Attention deficit
Sleep apnea	Snoring
Dental malocclusion	Depression
Occupational rhinitis	Irritability

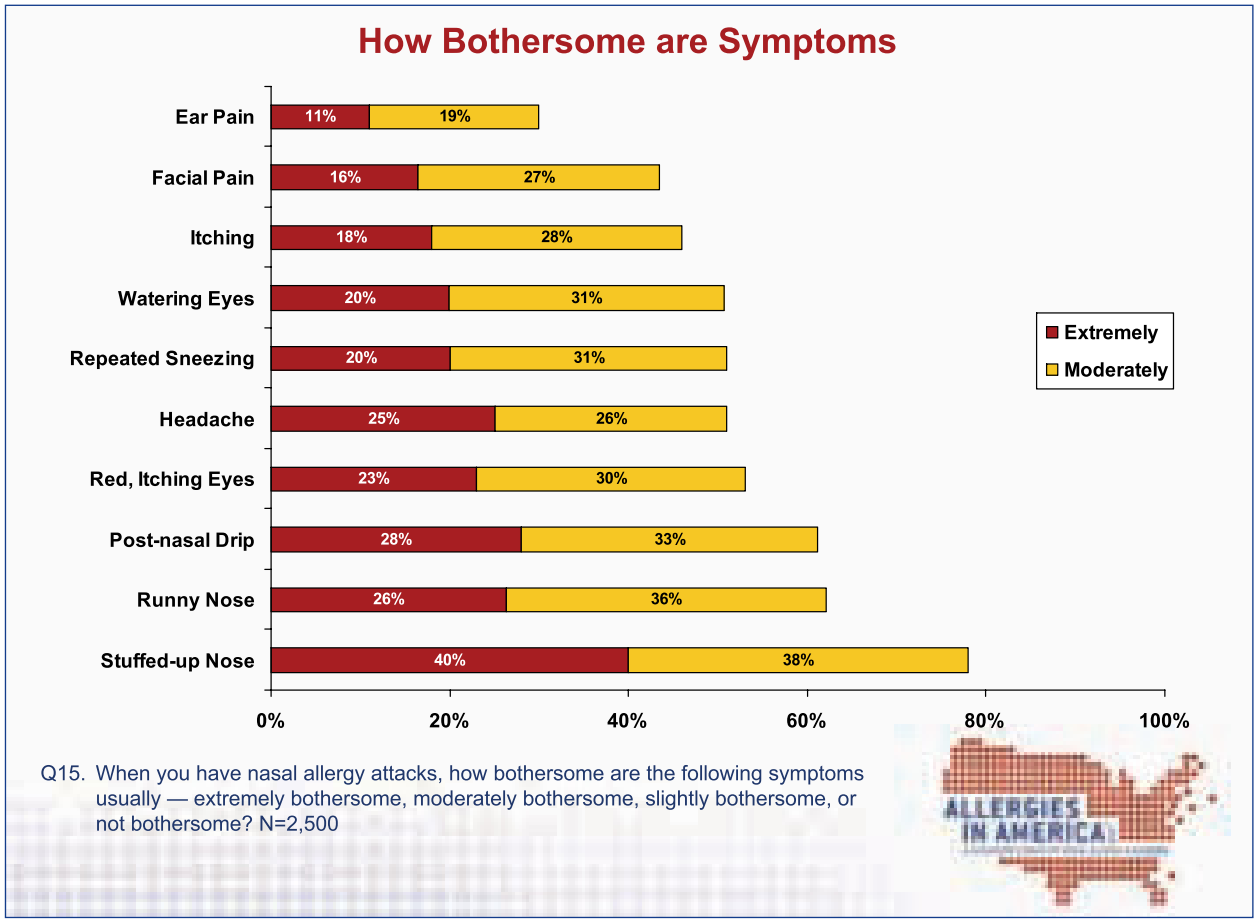


Figure 2 Allergies in America. A telephone survey conducted in 2500 adults with allergic rhinitis. Healthstar Communications, Inc., in partnership with Shulman, Ronca and Bucuvalas, Inc. Allergies in America: A landmark survey on nasal allergy sufferers. Executive summary. Florham Park, NJ: Altana Pharma US, Inc., 2006.

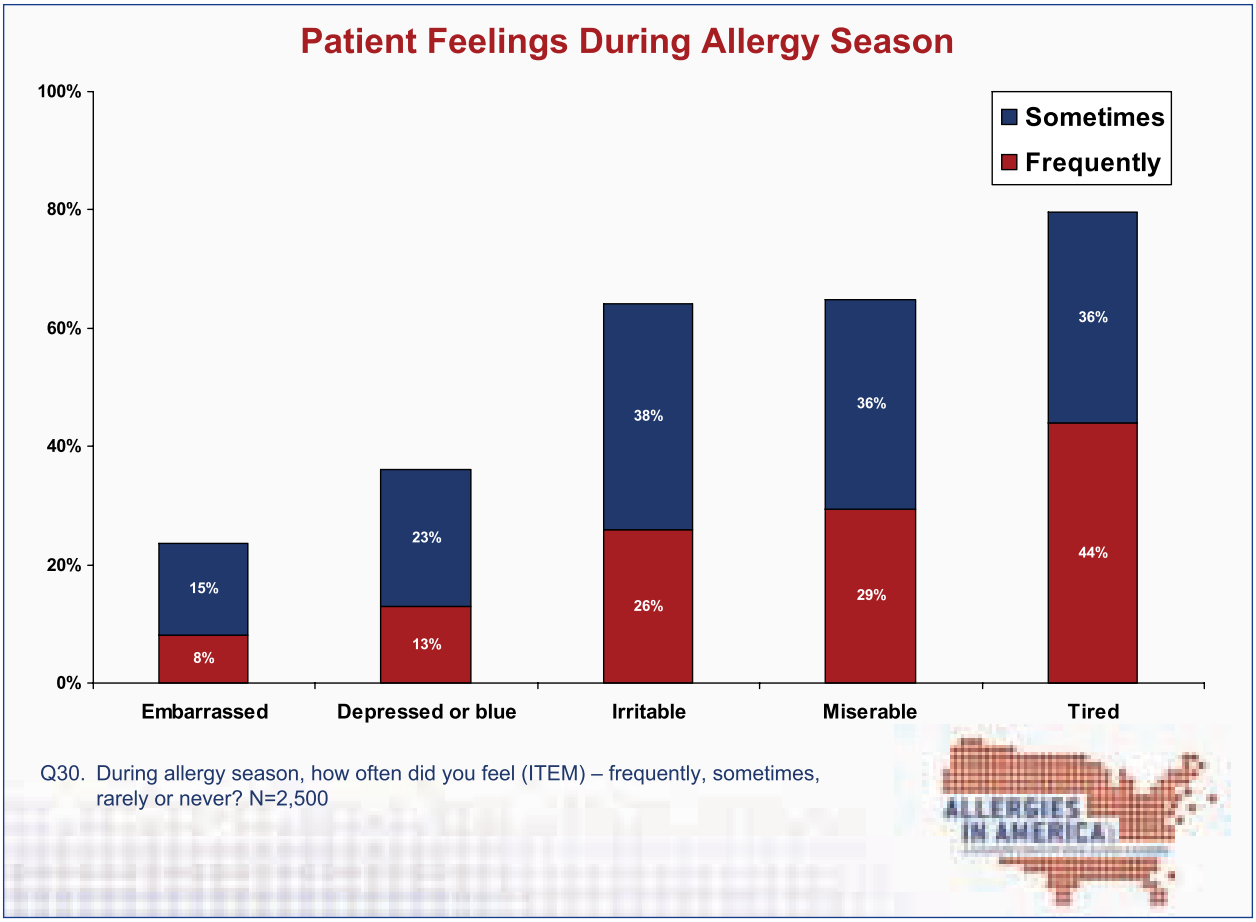
mostly devoid of major side effects. Topical (intranasal) glucocorticosteroids are one of the most effective modes of therapy for the majority of symptoms of AR. Intranasal dexamethasone was used over 40 to 50 years ago, however, today, inhalational corticosteroids, appropriately prescribed, are equally effective to dexamethasone and devoid of short- and long-term side effects. New to the repertoire of treatments available is a combined glucocorticosteroid - antihistamine for intranasal use, with superior effects than each molecule in isolation. Topical ipratropium bromide, is an excellent medication to control rhinorrhea and is mostly devoid of significant side effects. Other treatment modalities, including improved methods to administer intranasal saline, leukotriene inhibitors and blockers, as well as oral sympathomimetics can be of benefit to certain patients.

Sophisticated newer treatments, such as the use of monoclonal antibodies, may also benefit AR patients but will only be useful if costs are reduced.

Another treatment strategy is to induce tolerance to the allergens by allergen-specific subcutaneous or sublingual allergen immunotherapy (AIT). The aim of AIT is to induce tolerance to the allergens, with resolution of allergen-induced inflammation and symptoms.

CONCLUSION

In summary, appropriate treatment of AR is of paramount importance for the patient who suffers from this disease. The primary goal for any physician is to restore normal upper airway function and thereby control or prevent comorbidities and assure a normal quality-of-life. There is an old cliché which states “As goes the nose, so goes the chest”; if you appropriately treat AR, asthma is more easily controlled.



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2 MANAGEMENT OF ALLERGIC RHINITIS – ALLERGEN AVOIDANCE

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One of the components of allergy treatment is allergen avoidance, with total allergen avoidance leading to resolution of the allergen-driven inflammation and symptoms. Most environmental allergens are almost impossible to avoid, because they are either too prevalent or because it would seriously hamper professional or social life.

KEY MESSAGES

- During season one cannot avoid exposure to pollen allergens
- Exposure to mite allergen can be lowered but total avoidance is impossible
- Allergens of cats and dogs are ubiquitous
- Hypoallergenic animals do not exist

TREE, GRASS AND WEED POLLEN

Symptoms of pollen-induced AR occur upon exposure to pollen at the beginning of the season and disappear once the pollen season has finished. During the pollen season, total avoidance of exposure to pollen is hardly possible, unless patients emigrate to a country where the trees, grasses or weeds are not in bloom. Personal protection such as wearing sun glasses may reduce exposure in pollen allergic patients but most patients will be dependent on medication for symptom relief.

HOUSE DUST MITE

Dust mite allergen is present not only at home in beds, carpets and furniture but also in public spaces such as hospitals, public buses and cinemas (Figure 1). Total eradication is impossible. Encasings for mattresses, pillows and duvets reduce the amount of mite allergen but do not diminish symptoms. Special vacuum cleaners do contain the allergens but the user will be exposed to allergens while vacuum cleaning. Other measures such as washing on high temperatures kill house dust mites but do not prevent repossession of the fabric by the house dust mite. Essentially, the optimal situation at home will be a reduction of exposure by choosing non-fabric flooring and furniture, cleaning regularly and washing as much as possible at 55 degrees or higher. However, even if one manages to keep mite exposure at home to a minimum, exposure outside the home occurs and can evoke symptoms.

ANIMAL ALLERGENS

Animal allergens are to be found everywhere including the homes of people who themselves don't keep them. Exposure is also present in public transport and public places such as hospitals, buses, schools and pubs (Figure 1). Reducing allergen production by washing the animal has in case of cats been shown ineffective. The so called hypoallergenic animals such as the Labradoodle have been proven a myth: research showed that this dog produces normal amounts of allergen and that the allergen can be found in dust samples of the homes of their owners (Figure 2). Allergy to animals can not only hamper social life, it can force patients to change jobs, for instance laboratory workers developing allergies to rats or mice, with serious effects on income.

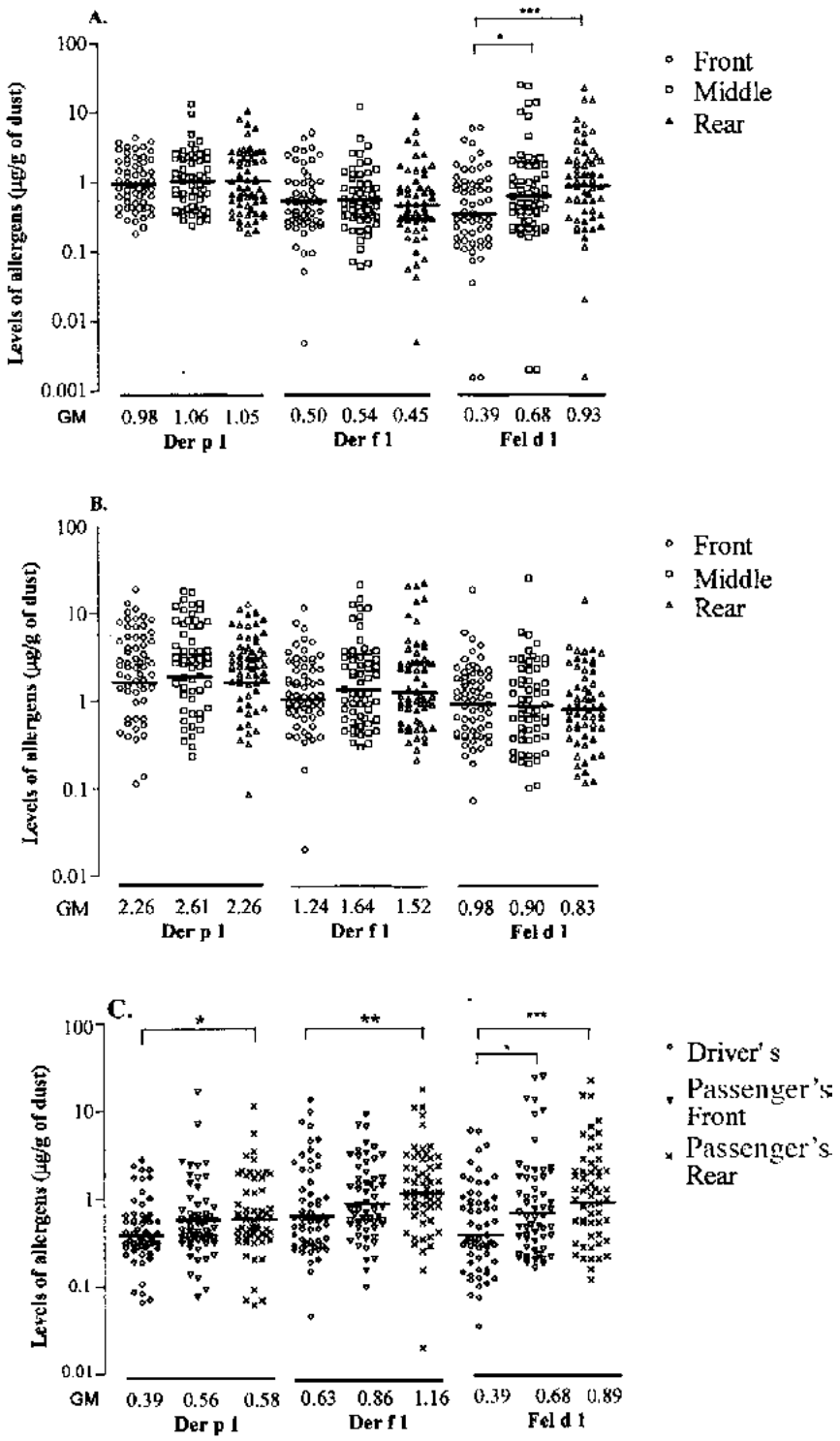

Figure 1 Levels of *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1), and *Felis domesticus* (Fel d 1) allergens in public transport vehicles. Dust samples were collected from front, middle, and rear seats in 60 natural-ventilation buses (A) and 60 artificial-ventilation buses (B) and from driver's, passenger's front, and passenger's rear seats in 60 taxis (C). Horizontal bars indicate geometric means (GMs); asterisks, P <.05; double asterisks, P <.01; and triple asterisks, P <.001. (*Reprinted from Ann Allergy Asthma Immunol, 93/2, Pereira FL, Silva DA, Sopelete MC, Sung SS, Taketomi EA. Mite and cat allergen exposure in Brazilian public transport vehicles. 179-184, Copyright 2004, with permission from Elsevier.*)

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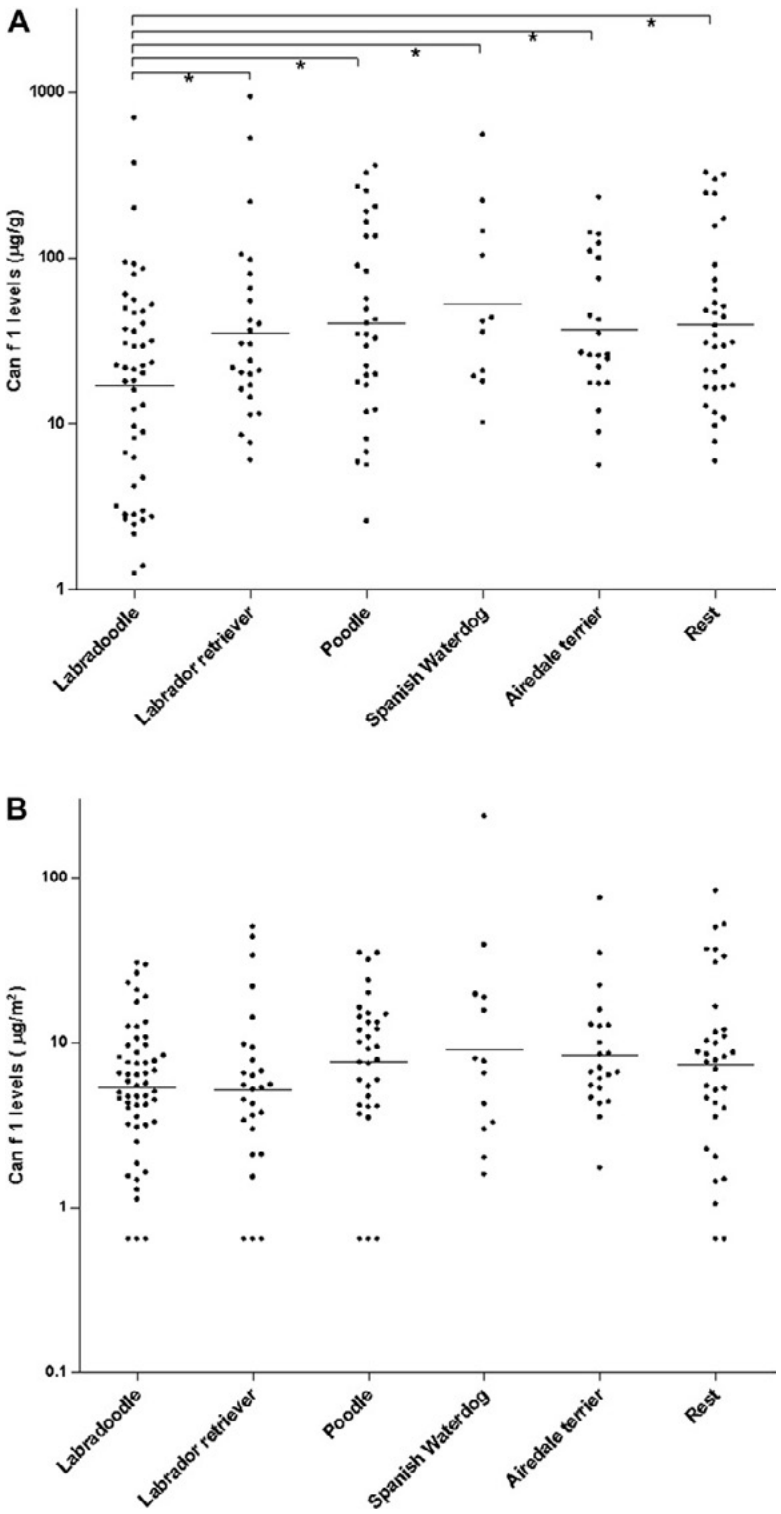

Figure 2 Can f 1 levels in SFD (A) and SAD (B) samples. Differences between breeds were tested for statistical significance in a multiple regression anal-ysis adjusted for type of floor (A) and sampling duration (days), type of floor, castration status of the dog, and time spent indoors by the dog (hours per day) (B). *P <.05. (*Reprinted from J Allergy Clin Immunol, 130/4, Vredegoor DW, Willemse T, Chapman MD, Heederik DJ, Krop EJ. Can f 1 levels in hair and homes of different dog breeds: lack of evidence to describe any dog breed as hypoallergenic. 904-909.e7, Copyright 2012, with permission from Elsevier.*)

3 ANTIHISTAMINES IN THE TREATMENT OF ALLERGIC RHINITIS

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KEY MESSAGES

- H_1-antihistamines are inverse agonists which 'turn off' the H_1-receptor and prevent its activation by histamine
- In allergic rhinitis, H_1-antihistamines are particularly effective in relieving histamine-mediated rhinorrhoea, itching, sneezing and vasodilation
- When used as monotherapy, H_1-antihistamines should be administered continuously while symptoms are present
- First-generation oral H_1-antihistamines, which readily diffuse into the brain, should not be used because of their detrimental central nervous system (CNS) effects. Second generation H_1-antihistamines have little or no CNS effects but somnolence may occur with some drugs in some cases

H_1-antihistamines are inverse agonists of the histamine H_1-receptor. The H_1-receptor, like other G-protein coupled receptors, is essentially like an electric switch that is turned on by histamine and off by antihistamines. At the molecular level, the proportion of H_1-histamine receptors that are in the 'turned off' configuration, which is never 100%, is dependent on the local H_1-antihistamine drug concentration.

To understand the potential role of H_1-antihistamines in allergic rhinitis (1) it is necessary to recap the effects of histamine in this condition. The initial event in AR is the interaction of allergen, with mast cell bound IgE. The histamine released in the resultant degranulation is primarily responsible for the early phase symptoms. These symptoms, shown in green in Figure 1, are rhinorrhoea, itching, sneezing and vasodilation. Mast cell-derived cytokines initiate allergic inflammation in which the influx and activation of eosinophils results in accentuation of local nerve reflexes to cause nasal blockage (red in Figure 1) and reflex mediated conjunctival symptoms. Considering these mechanisms, H_1-antihistamines are particularly effective against the histamine-mediated early phase symptoms of AR. All H_1-antihistamines also have weak anti-inflammatory activity and so have some effect on nasal blockage. However, this is slow in onset (weeks) and weak compared with nasal corticosteroids.

ARIA recommends avoidance of first-generation oral H_1-antihistamines which readily diffuse into the brain. Histamine is an important neurotransmitter in the brain where it increases arousal in the circadian sleep/wake cycle and reinforces learning and memory. These effects are blocked by first-generation H_1-antihistamines, which also reduce the du-

TABLE 1

Common H_1-Antihistamines
1st Generation Antihistamines
Diphenhydramine
Chlorpheniramine
Hydroxyzine
2nd Generation Antihistamines
Cetirizie
Loratadine
Fexofenadine
Desloratadine
Levocetirizine
Rupatadine
Bilastine
Topical Antihistamines
Azelastine
Olopatadine

ration of REM sleep when taken at night (Figure 2). Furthermore, the long half-lives of drugs such as diphenhydramine, chlorpheniramine and hydroxyzine, ≈24 hours, mean that these effects are still present next morning leading to daytime somnolence, increased traffic accidents, decreased productivity at work and reduced children's learning. Second-generation H_1-antihistamines are largely devoid of these effects.

H_1-antihistamines may be administered either orally or topically. Given orally, their onset of action is in 1–4 hours and once a day dosage is usually sufficient. Most second generation H_1-antihistamines have little or no central nervous system effects but somnolence may occur with some drugs in some patients. Intranasal antihistamines have the advantage of rarely causing systemic effects but have the disadvantages of twice-daily dosage and being less convenient than tablets. Used as monotherapy, H_1-antihistamines should be administered continuously while symptoms are present. Alternatively, the may be used intermittently for symptom exacerbations in individuals being treated with intranasal corticosteroids.

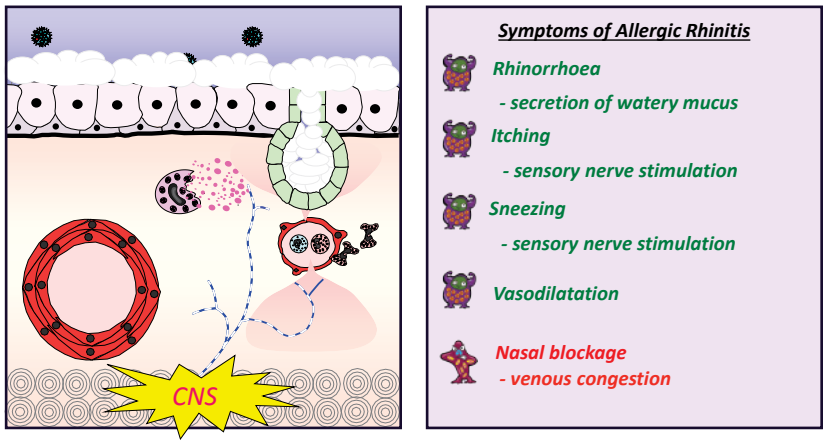

Figure 1 Diagrammatic representation of the symptoms of allergic rhinitis showing mucus secretion, sensory nerve activation and vasodilatation. In and close to the post-venular capillary below the mucous gland, inflammatory leukocytes, particularly eosinophils are accumulating to initiate allergic inflammation. On the right is a list of the main symptoms of allergic rhinitis. Those in green, alongside the figure of a mast cell, are primarily histamine-induced and particularly sensitive to blockade by H1-antihistamines. Nasal blockage, in red alongside the figure of an eosinophil, is not histamine-mediated and is only weakly blocked by H1-antihistamines.

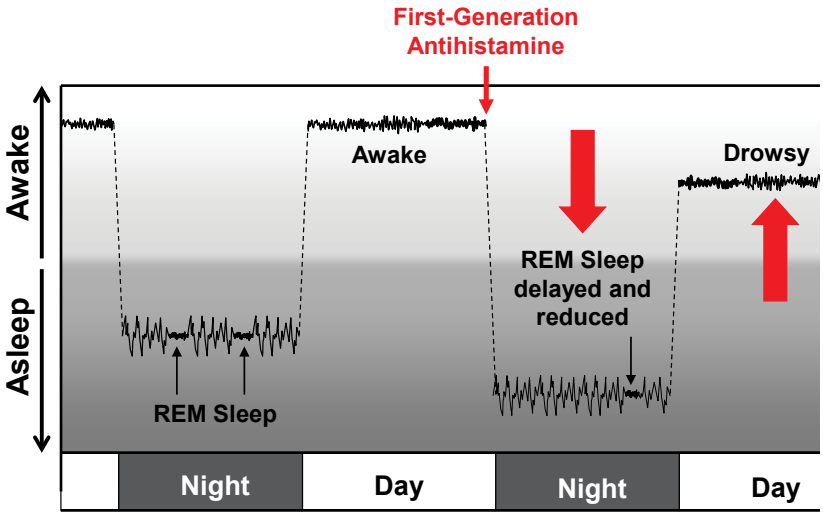

Figure 2 Diagrammatic representation of the effect of first-generation H1-antihistamines on the electrical activity of the brain. There are approximately 64,000 histamine-producing neurones, located in the tuberomamillary nucleus of the human brain that influence arousal in the circadian sleep/ wake cycle. Blockade of this system results in delayed and reduced rapid eye movement (2) sleep and subsequent daytime somnolence

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4 TREATMENT OF ALLERGIC RHINITIS – NASAL STEROIDS

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KEY MESSAGES

- Intranasal steroids (INS) are the most effective medication class in controlling the symptoms of allergic rhinitis (AR)
- INS may provide significant relief of symptoms of intermittent or persistent AR
- The overall clinical response does not appear to vary significantly between available INS, irrespective of the differences in topical potency, lipid solubility, and binding affinity
- When given in recommended doses INS are not associated with clinically significant systemic side effects

The main mechanism by which intranasal steroids (INS) relieve the symptoms of allergic rhinitis (AR) is through their anti-inflammatory activity, although it is possible that they may exert an effect through other non genomic mechanisms. The rationale for using INS in the treatment of AR is that high drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects.

INS are effective in controlling all the four major symptoms of AR: sneezing, itching, rhinorrhea and especially nasal congestion. They also control the ocular symptoms of rhinoconjunctivitis.

Meta-analyses confirmed that INS are the most effective therapeutic agents for AR (Table 1). INS are superior or equal to the combination of an antihistamine and an antileukotriene. ARIA Guidelines 2010 recommend INS for treatment of AR in adults (strong recommendation | high quality evidence) and suggest INS in children with AR (conditional recommendation | moderate quality evidence). This recommendation places a relatively high value on the efficacy of INS, and a relatively low value on avoiding their possible adverse effects.

Due to their mechanism of action, efficacy appears after 7–8 h of dosing, but maximum efficacy may require up to 2 weeks. However, some patients benefit within the first 2 hours.

The general characteristics of the formulations of INS and recommended doses in children and adults are shown in Table 2.

Systematic reviews compared INS to other active treatments and reported a low incidence of adverse effects. Epistaxis, headache, abnormal taste, and pharyngitis were the most frequently reported side effects. None of the short-term treatment studies analyzed in the reviews reported systemic side effects from INS, although there has been concern that their prolonged use may be associated with systemic adverse effects including suppression of the hypothalamic-pituitary-adrenal axis and suppression of growth in children. Recently, it has been shown that fluticasone furoate administered over 52 weeks in prepubescent children resulted in a small reduction in growth velocity compared with placebo.

Patient education on the proper administration technique is very important since the incorrect use leads to treatment failure or adverse events such as epistaxis (in 10-15% of patients).

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TABLE 1

Benefits and harms of treatments for allergic rhinitis

	Benefit	NNT	Harm	NNH
Antihistamine				
Class mean	0.07	15.2	0.02	51
Nasal corticosteroid spray				
Class mean	0.23	4.4	0.02	48
Nasal antihistamines				
Azelastine (daily)	0.16	6.3	0.03	32
Azelastine (twice daily)	0.20	5.0	0.05	22
Other				
Montelukast	0.07	14.3	0.01	167
Omalizumab	0.08	12.3	0.08	13
Immunotherapy	0.22	4.6	0.07	14

NNT=number needed to treat to make one person better. NNH=number needed to harm to make one adverse event arise. A high number in the benefit section indicates a great benefit. A high number in the harm section indicates the most harm. The major adverse events were epistaxis for nasal steroids and sedation for antihistamines.

Data from Greiner A, Hellings P, Rotiroti G, Scadding G. Allergic rhinitis. Lancet 2011;378:2112–2122.

TABLE 2

General characteristics of the formulations of intranasal steroids, age from which they can be used in allergic rhinitis, and corresponding dosages for children and adults.

Name	Formulation	Minimum age	Dose per spray mcg*/nostril	Maximum dose/ children mcg/day	Dose/adults mcg/day
Triamcinolone acetonide	Isotonic	4 years	55	110	220
Budesonide	Isotonic	6 years	32, 50, 64, 100	100	200
Ciclesonide	Hypotonic	6 years	50	100	200
Beclomethasone dipropionate	Isotonic	6 years	50	100	200
Mometasone furoate	Isotonic	2 years	50	100	200
Fluticasone propionate	Isotonic	2 years	50	100	200
Fluticasone furoate	Isotonic	4 years	27.5	52.5	105

**mcg micrograms. Source: Medication inserts.*

Modified from Mello Jr JF, Mion Ode G, Andrade NA, Anselmo-Lima WT, Stamm AE, Almeida WL, et al. Brazilian Academy of Rhinology position paper on topical intranasal therapy. Braz J Otorhinolaryngol 2013;79:391-400.

5 ANTILEUKOTRIENES IN THE TREATMENT OF ALLERGIC RHINITIS

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KEY MESSAGES

- Cysteinyl leukotrienes are released during early and late allergic inflammation of the nasal mucosa from mast cells and eosinophils
- Many nasal symptoms of oedema, congestion, secretion and infiltration are mediated by the activation of CYSLT1 receptor but other receptors to cysteinyl leukotrienes are postulated
- Currently, only CYSLT1 receptor antagonist are recommended as add-on therapy of allergic rhinitis (AR); montelukast is the best studied one and its efficacy seems better for moderate to severe persistent disease
- Novel inhibitors of 5-lipoxygenase or its activating protein (FLAP) are under development which may improve benefits of antileukotriene therapy in AR

Cysteinyl leukotrienes (CysLTs) were discovered as potent mediators in asthma but participate also in the early and late allergic allergic inflammation of the nasal mucosa (Figure 1). This family of oxylipins produced by 5-lipoxygenation (5-LO) of arachidonic acid include peptide derivatives (LTC_4, LTD_4 and LTE_4) and the chemoattractant LTB_4 (Figure 2). CysLTs are synthesized by activated mast cells and eosinophils. However, a transcellular synthesis is also possible by neutrophils releasing the unstable intermediate LTA_4 and by neutrophil-adhered platelets expressing leukotriene C_4 synthase. CysLTs are pro-inflammatory mediators leading to increased vascular permeability and oedema of nasal mucosa, mucus secretion, and chemoattraction of eosinophils and lymphocytes T. CysLTs also constrict the bronchial tree and augment airway hyperreactivity and remodelling. Many respiratory symptoms elicited by CysLTs are mediated by the activation of type-1 receptor (CysLT1R), although the presence of other receptors for CysLT in the respiratory system has been postulated.

Two classes of leukotriene modifying drugs are currently available (Figure 2). 5-lipoxygenase inhibitor zileuton prevents LTA_4 production, whereas antagonists of $CysLTR_1$ (zafirlukast, pranlukast and montelukast) abates CysLTs signalling by CysLT1R (Table 1). Inhibition of 5-lipoxygenase was found beneficial in AR as early as in 1990, however, randomized control trials (RCTs) were published only on montelukast. A comprehensive review described a decrease in daytime nasal symptoms in AR patients treated with montelukast versus placebo in 5 out of 6 RCTs. In addition, combined therapy with montelukast and loratadine or with topical steroids also showed improvement of daytime AR symptoms. Beneficial effects were experienced both by patients with seasonal and perennial AR. The 6th RCT included in the analysis, comparing montelukast as add-on to intranasal fluticasone propionate monotherapy, failed to show advantages in patients with intermittent AR during 6 weeks of treatment. Currently, montelukast is recommended in moderate to severe AR as a combination with intranasal corticosteroids and/or oral antihistamines. The indication is supported by a recent RCT on subjects sensitized to perennial mites allergen showing benefits of add-on montelukast over nasal fluticasone propionate

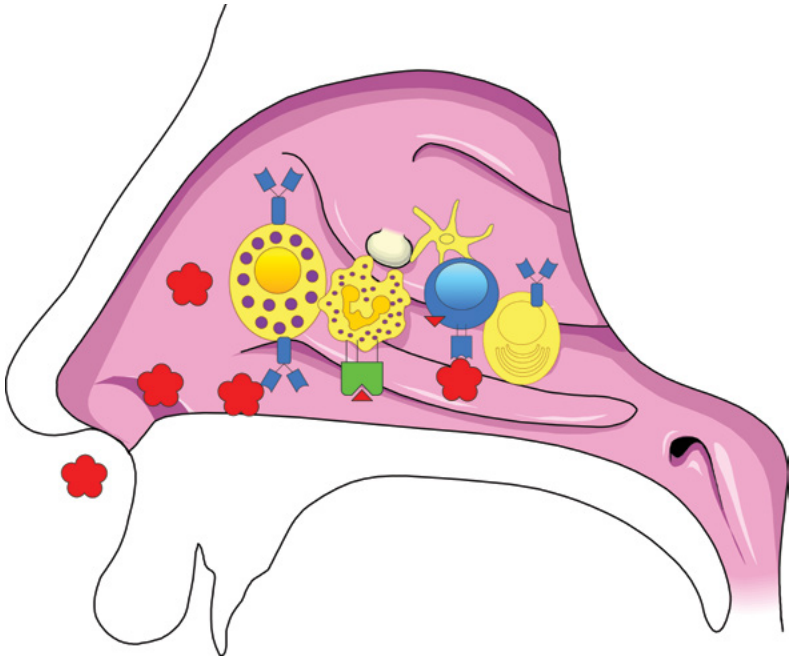

Figure 1 Exposure to aeroallergens perpetuates allergic inflammation by continuous production of specific IgE, degranulation of mucosal mast cells (early phase) and release of chemical mediators (chemokines, CysLTs) by activated mast cells, eosinophils and lymphocytes-T. Since CysLTs act in concert with other cytokines, no significant impact on AR is expected using antileukotrienes monotherapy.

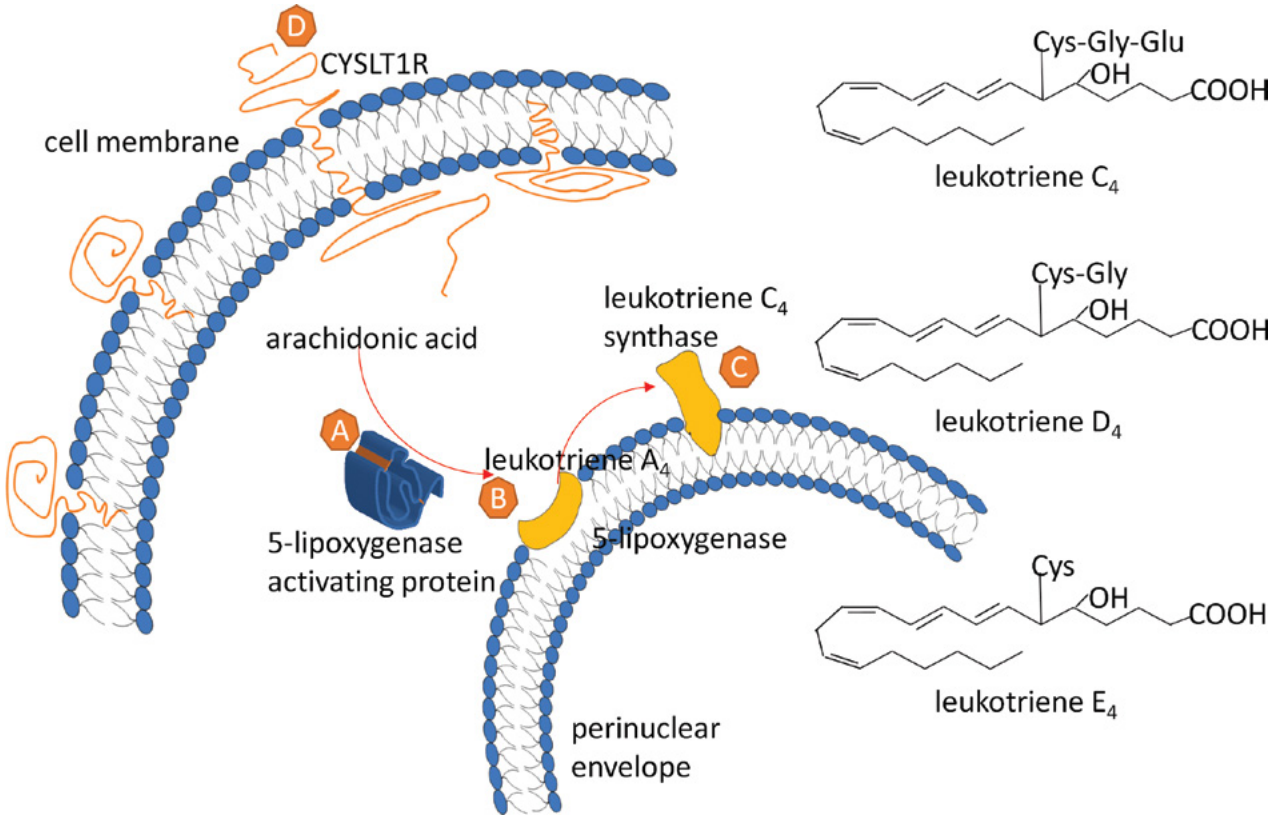

Figure 2 Arachidonic acid is released from cell membranes by calcium-dependent cytosolic phospholipases and transported by FLAP to 5-lipoxygenase present at nuclear envelope. Only some myeloid cells are capable to release high amounts of CysLTs due to expression of leukotriene C_4 synthase. Many nasal symptoms are mediated by the activation of CYSLT1R, including the autocrine activation of mast cells. Novel inhibitors of FLAP (1: licofelone, veliflapon), 5-lipoxygenase (2: atreleuton, setileuton, flavocoxid), LTC_4 synthase (3: TK04) are under development in addition to CYSLT1R antagonists.

TABLE 1

Antileukotriene drugs currently available on the market

Name	Mechanism of action	Indications	Age limit	Administration	Adverse effects
Zileuton (Zyflo)	15-LO inhibitor	asthma	adults	b.i.d (extended release version) or q.i.d	dyspepsia (8.2%), transaminases elevation (1.9%)
Montelukast (Singulair, Pluralair, Montecarlo, Lovetas)	CysLT1 antagonist	asthma, rhinitis	adults and children from 6 months on	q.d	not observed
Pranlukast (Onon, Azlaire)	CysLT1 antagonist	asthma, rhinitis	adults and children from 1 year on	b.i.d	not observed
Zafirlukast (Accolate)	CysLT1 antagonist	asthma, rhinitis	adults children from 5 years on	b.i.d	not observed (hepatoxicity single reports)

Abbreviations: bid = twice per day, qd = once daily; qid = four times per day; LO = lipoxygenase; LT = leukotrienes

TABLE 2

Novel antileukotriene drugs under investigation in clinical trials

Name	Action	Indications	Development stage	Adverse effects
Veliflapon	FLAP inhibitor	myocardial infarction, stroke	phase III suspended	serum LDL, creatinine elevations
Licofelone	FLAP inhibitor/ COX inhibitor	osteoarthritis	phase III	not observed
GSK2190915	FLAP inhibitor	asthma	phase II	not observed
Atreleuton	15-LO inhibitor	atheromatosis, cardiovascular disease	phase II	not observed
Setileuton	15-LO inhibitor	asthma, COPD, cardiovascular disease	phase II	transaminases elevation
Flavocoxid (pharmaceutical plant flavonoid)	15-LO inhibitor/COX inhibitor	arthritis	phase II	hepatotoxicity
TH04	LTC4 synthase inhibitor	preclinical	preclinical	unknown

Abbreviations: COX = cyclooxygenase; FLAP = 5-lipoxygenase activating protein

monotherapy, measured not only as a decrease in symptoms score but also as an improvement in the Rhinoconjunctivitis Quality of Life Questionnaire and loratadine rescue self-administration. In addition eye symptoms and night-symptoms improved, with the greatest effect by the end of the two-months trial.

In summary, selective targeting of the CysLTs pathway is not expected to bring spectacular improvement in AR. However, addition of a CysLT1R antagonist is effective in moderate/severe persistent AR following regular treatment during at least two months. The inhibition of 5-LO or 5-LO activating protein (FLAP) might potentiate the effects of antileukotriene therapy of AR, however, drugs with a satisfactory pharmacokinetics are still under development (Figure 2, Table 2).

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6 ADDITIONAL DRUG TREATMENT OPTIONS FOR ALLERGIC RHINITIS

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KEY MESSAGES

- Due to inadequate response to regular medical treatment, up to 20 percent of allergic rhinitis (AR) patients may need additional medical treatment to control their symptoms
- In AR with persistent nasal obstruction despite topical steroids, a short course of nasal decongestants or oral steroids may be recommended
- In patients with persisting rhinorrhea, add-on topical anticholinergics are the treatment of choice
- Nasal cromones may be an alternative choice in small children and in pregnancy, where adherence to standard treatment is questionable

Allergic rhinitis (AR) is not well controlled in up to 20% of the patients despite adequate medical treatment. Lack of control is commonly related to the poor adherence to treatment, however, non-specific nasal hyperreactivity, upper airways comorbidities and insufficient control of environmental/endogenous factors may also play a role.

In uncontrolled patients additional drug treatment options, aiming to improve control of remaining symptoms include oral and nasal decongestants, nasal anticholinergics, cromones and systemic steroids (Figure 1 and Table 1).

Nasal and oral decongestants markedly improve nasal obstruction, however, due to mainly local adverse effects, treatment with decongestants is limited to a very short course treatment.

Topical mast cell stabilizers, like cromones, have been proven higher efficacy for the treatment of ocular rather than nasal symptoms. Topical nasal cromones can safely be presribed to small children and in pregnancy, however, due to low efficacy compared to topical and oral H1 antihistamines, they are not strongly recommended as the first line treatment of AR. Cromones taken several hours prior to to allergen exposure may prevent symptoms of the early phase reaction. As they should be taken 4 times daily, adherence to cromones is poor.

Nasal anticholinergics, like ipratropium bromide, has proven efficacy in the control of rhinorrhea, however, as it is the only symptom which is significantly reduced compared to placebo, topical anticholinergics are considered as an additional treatment when control of rhinorrhea is not achieved by maximal standard treatment with the combination of topical steroids and H1 antihistamines.

Systemic steroid treatment in patients unresponsive to maximal standard medical treatment is limited to a short course of oral corticosteroids, and avoidance of intramuscular administration is strongly recommended due to risk of local and systemic side effects. The adverse events of a short course of oral steroids is acceptable in most of uncontrolled patients. Its efficacy was not adequately evaluated in high quality trials. Major improvement after oral steroid treatment are the reduction of nasal obstruction and smell improvement in patients unresponsive to topical steroids, including those who have been on prolonged treatment with decongestants.

In patients with uncontrolled AR despite adherence to nasal steroids,

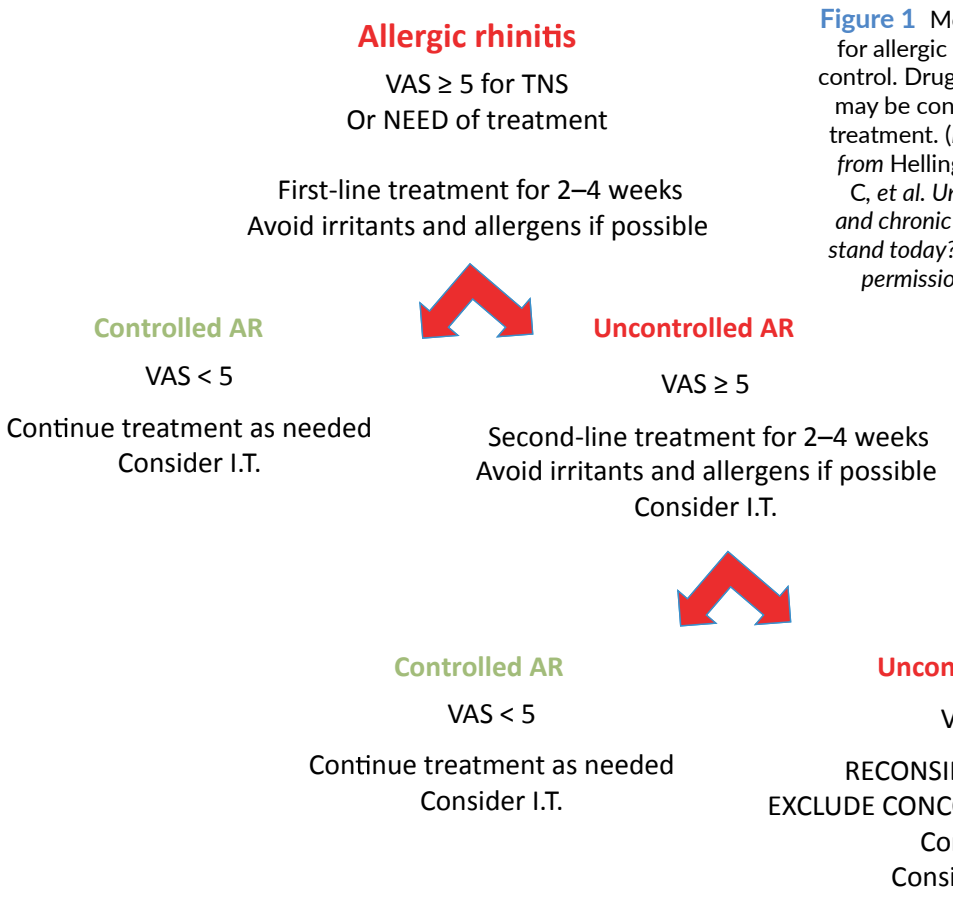

Figure 1 Modified treatment algorithm for allergic rhinitis to achieve disease control. Drugs mentioned in this chapter may be considered as the second line treatment. (*Reproduced with permission from* Hellings PW, Fokkens WJ, Akdis C, *et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today?. Allergy, 2013;68:1-7, with permission from Willey Blackwell.*)

TABLE 1

Efficacy and safety of additional treatments in allergic rhinitis. Safety is estimated in terms of short-term treatment

	congestion	rhinorrhea	sneezing	nasal itch	ocular itch	safety
nasal decongestant	++	0	0	0	0	+
oral decongestant	++	0	0	0	0	+
nasal cromone	+	+	+	+	+	+++
ocular cromone	0	0	0	0	+	+++
nasal anticholinergic	+	+++	0	0	0	++
oral steroid	+++	+++	+++	++	++	+

Efficacy of different drugs is adapted according to the ARIA 2001 recommendations.

a short course of nasal/oral decongestants followed by short course of oral steroids may be prescribed. In patients with persisting rhinorrhea, added topical anticholinergics are the treatment of choice. Nasal cromones may be an alternative choice in small children and in pregnancy, where adherence to standard treatment is questionable (Figure 1 and Table 1).

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7 CONSERVATIVE NON-DRUG TREATMENT FOR ALLERGIC RHINITIS

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KEY MESSAGES

- Nonpharmacological treatment options for allergic rhinitis gain popularity and may be applied alone or complementarily
- Apart from isotonic and hypertonic nasal sprays, which are already widely used, alternative methods, such as thermal water applications, endonasal phototherapy or acupuncture are available and have been investigated in clinical trials
- Although the exact mechanism of action is not yet fully understood, clinical evidence assigns similar efficacy to nonpharmacological treatments compared to traditional agents with hardly any side effects

Giving credit to a worldwide growing acceptance of herbal products and simultaneously limited efficacy of conservative pharmacological agents, nonpharmacological treatment options – alone or complementary – have become popular and widely investigated in clinical trials in allergic rhinitis (AR).

While isotonic and hypertonic nasal sprays, based on a great variety of active agents such as liposomes, ectoine, herbal compounds, cellulose, and vaseline are already widely used, alternative methods such as thermal water applications, endonasal phototherapy or even acupuncture are also gaining more importance. The mechanisms of action are of different nature (Figures 1 and 2). Nasal sprays and nasal irrigations unfold their effect by implementing by creating a hydrofilm as a mechanical barrier. They thus aim to strengthen resistance to airborn allergens and iritants.

Saline nasal irrigation belongs to those complementary non-pharmacologic treatment options with a relieving effect on symptoms of the AR. A meta-analysis of 10 studies investigated its' effect as adjuvant therapy. Nasal symptoms were reduced by 27.66%, while simultaneously less rescue medication (-62.1%) was applied and the patient's quality of life was improved (+27.88%).

Likewise, in a meta-analysis, an ectoine-based nasal spray has been shown to reduce the severity for all relevant rhinitis symptoms to the same extent as traditional agents. Nasal obstruction, rhinorrhea, and itching eyes improved by 29.94%, 31.49%, and 33.49%.

Similarly, the nasal administration of liposomes was also compared with guideline-recommended therapeutic regimes in several small open-label trials. The liposomal sprays showed good results in clinical tolerability as well as in reducing typical rhinitis symptoms.

Thermal water irrigations and inhalations offer a new additional approach in AR despite having a century-old tradition in Roman practices. A systematic review revealed that nasal flow, nasal resistance and mucociliary clearing time were significantly improved using thermal water applications while only little side effects were documented.

A fairly new concept is an endonasal phototherapy with rhinolight, utilizing the immunosuppressive effects of UV radiation by directing UV-A, UV-B and visible light into the nasal cavity (Figure 3). Although its effectiveness has been demonstrated in clinical studies, the risk of damaging the mucosa has not been assessed sufficiently.

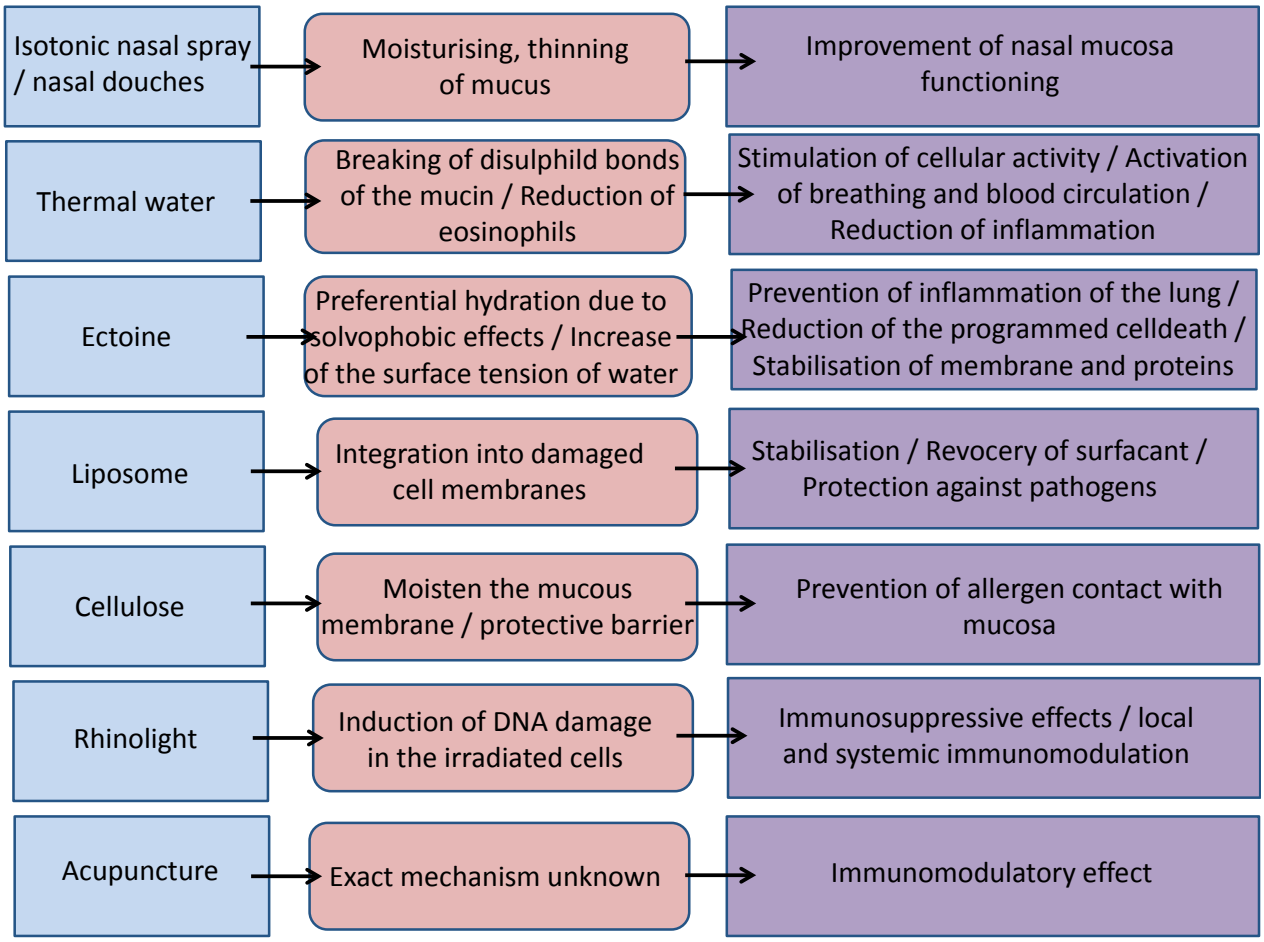

Figure 1 Mechanism of action for different non-pharmacological treatment agents.

In summary, compared to standard therapy, alternative therapies have shown efficacy with limited or no side effects. Nevertheless, the operating principles of new therapeutic approaches must be further explored and evaluated in the future. Comparing the efficacy of alternative therapies with standard effective treatment is warranted.

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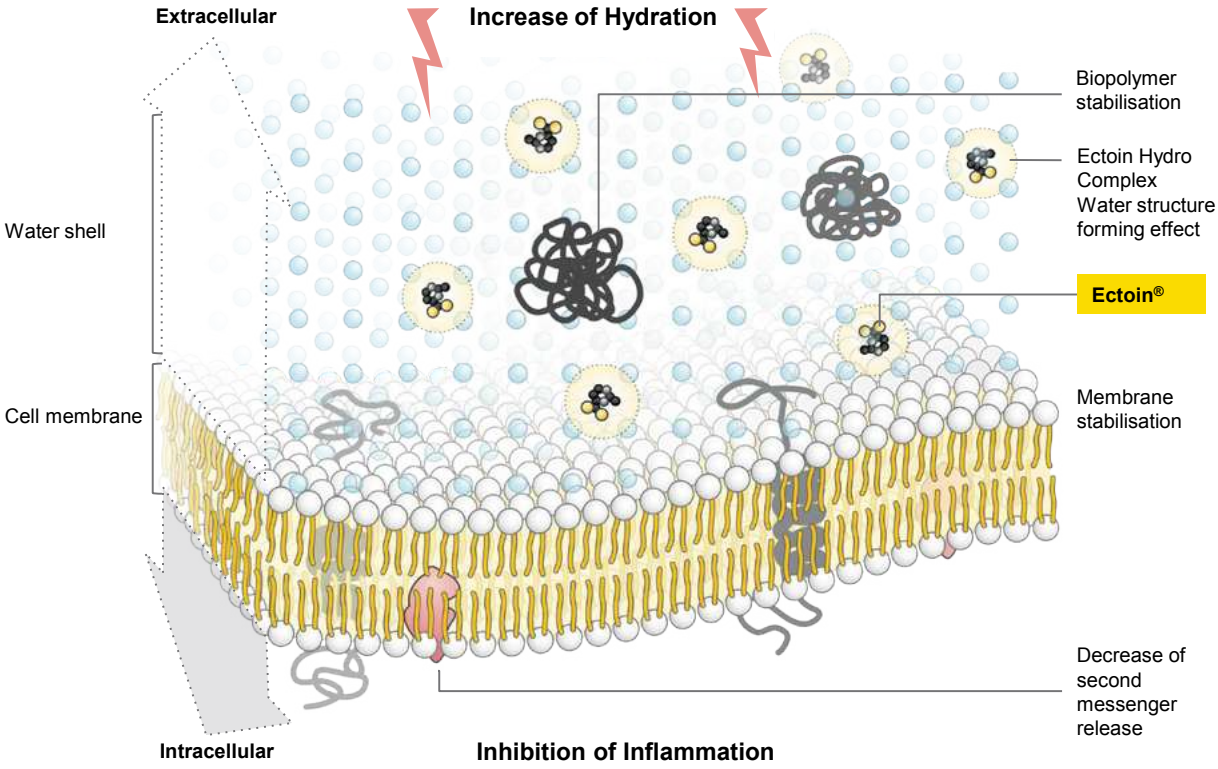

Figure 2 Protective and hydrating properties of ectoine. (*From bitop AG-Extremolytes for Life, Ectoin – mode of action; reprinted with permission of bitop AG, Germany.*)

Figure 3 Application of endonasal phototherapy with rhinolight® device. (*From Rhinolight Ltd. rhinolight broschure – Clinically proven phototherapy of allergic rhinitis, p.3; reprinted with permission of Rhinolight Ltd., Hungary.*)

8a ALLERGEN IMMUNOTHERAPY FOR ALLERGIC RHINITIS - OVERVIEW

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KEY MESSAGES

- Allergen immunotherapy (AIT) is an immune-modulating therapy aiming at restoring normal immunity against allergens
- The balance between IL-4-secreting T helper 2 cells and IL-10-secreting inducible T regulatory cells is central for the AIT-induced long-term immune tolerance of allergens
- AIT is indicated for the treatment of moderate-to-severe intermittent or persistent allergic rhinitis (AR)
- AIT shows pharmacoeconomic advantages over other treatments for AR and plays a key role in the prevention of new sensitisations and asthma

MECHANISMS

Allergen immunotherapy (AIT), which represents the only specific approach to the treatment of allergic rhinitis (AR) provides a unique opportunity to specifically restore normal immunity against allergens and affect the long term course of AR. AIT triggers multiple sequentially activated mechanisms, which work in concert leading to clinical events eliciting rapid desensitization to allergen, long-term allergen-specific immune tolerance as well as the suppression of allergic inflammation.

AIT induces a shift in the proportion of IL-4-secreting T helper (Th) 2 cells in favor of IL-10-secreting inducible T regulatory cells (iTreg) specific for the same allergenic epitope, which increase in number and function. Different types of iTreg control several facets of allergic inflammation. They are composed of $FOXP3^+$ (Forkhead box protein 3) adaptive T regulatory (Treg) cells and FOXP3 negative, but IL-10-producing Tr1 cells. A significant correlation is found between improvement of symptoms and the increase in Treg cell numbers during AIT. Recently the B regulatory cells (B reg) characterized as $CD73^-CD25^+CD71^+$ cells were found in increased numbers in subjects undergoing AIT. Breg cells regulate IgG4 versus IgE and induce allergen-specific antibodies towards the non-anaphylactic and non-inflammatory type. The shift in isotype production cannot however, explain the therapeutic effect of AIT probably due to a very long IgE lifespan. iTregs suppress allergen-specific T cells in both their regulatory and effector functions. T cell suppression can take place both in the secondary lymphoid organs and in the affected tissues. iTreg are also capable of suppression of innate effector cells of allergic inflammation (mast cells, basophils) and induce decrease of eosinophils in the mucosal tissues. The understanding of the AIT mechanisms helps in elaboration of early and late diagnostic biomarkers to select the best responders and to optimize the treatment.

INDICATIONS AND EFFICACY

AIT is indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of AR. Usually AIT is recommended in subjects over 5 years of age, however sublingual AIT is safe and effective even in children as young as 3 years of age. The recommended duration of AIT for AR is 3 years, both for the subcutaneous and the sublingual routes.

Significant improvement in nasal and ocular symptom scores, reduced need for symptomatic

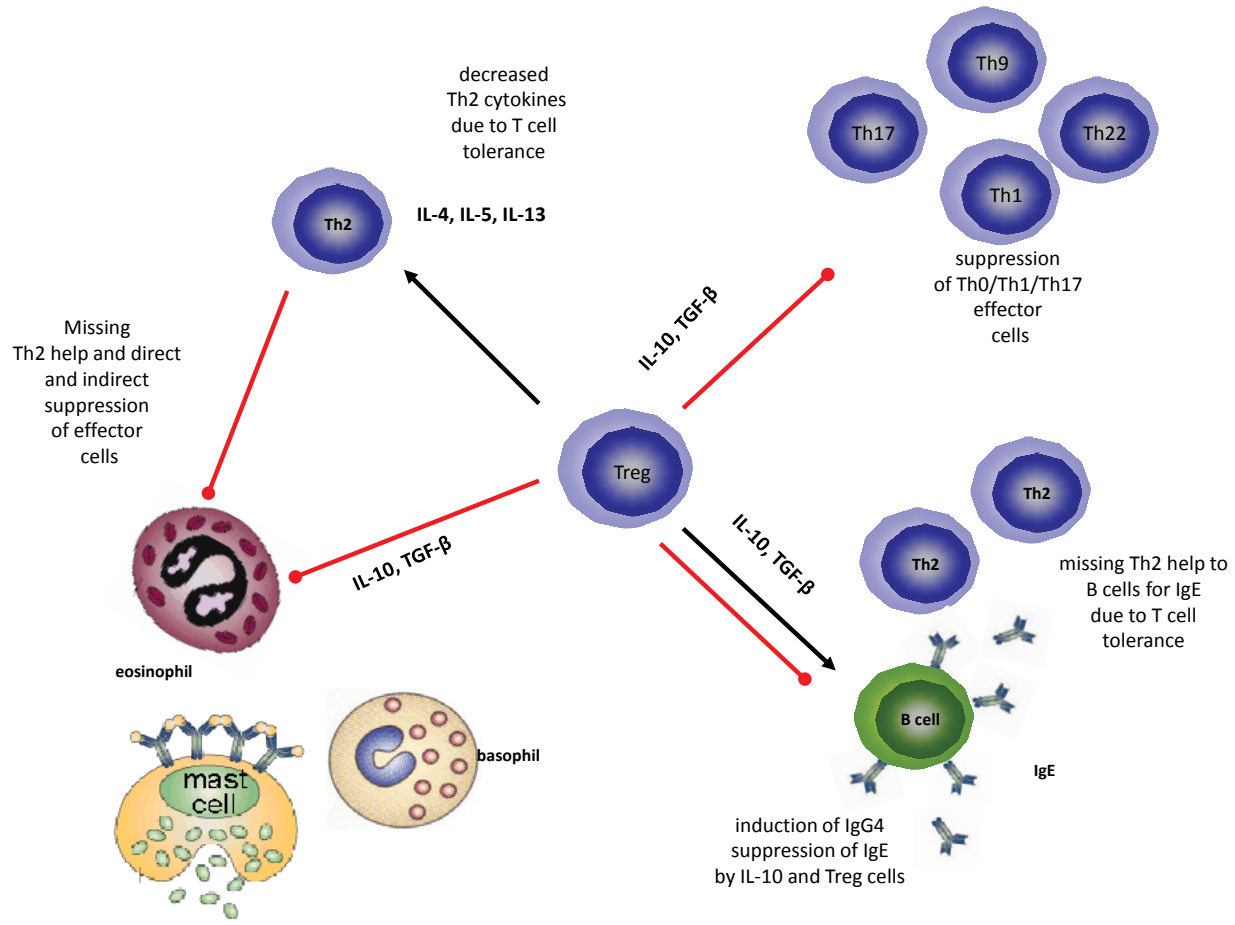

Figure 1 After the first administration of the AIT vaccine, there is an early decrease in mast cell and basophil degranulation. Treg cells are generated and there is suppression of allergen-specific Th2 cells and other effector cells. Suppression of IgE production, endothelial cell activation and Th2 cell homing to tissues, mucus production by the epithelium, and tissue migration, priming and survival of mast cells, eosinophils and basophils appears. IL-10 and TGF-β directly and indirectly regulate B cells and effector cells. A decrease in tissue mast cells and eosinophils and release of their mediators and decrease in late phase response is observed in the affected tissues (red arrows: suppression, black arrows: induction). AIT = allergen immunotherapy; IL= interleukin; TGF= transforming growth factor; Th= T helper cells; Treg = T regulatory cells

medication and improved quality of life both during and after discontinuation of AIT has been consistently demonstrated in double-blind placebo-controlled studies. The major advantage of AIT in the treatment of AR is the prevention of asthma and the reduction of new sensitizations.

AIT should only be performed with standardized allergen extracts, which are currently available for grass, tree, and weed (ragweed, mugwort) pollens; house dust mites; several mold species and animal dander. Pharmacoeconomic studies demonstrated a clear advantage of AIT over pharmacologic therapies.

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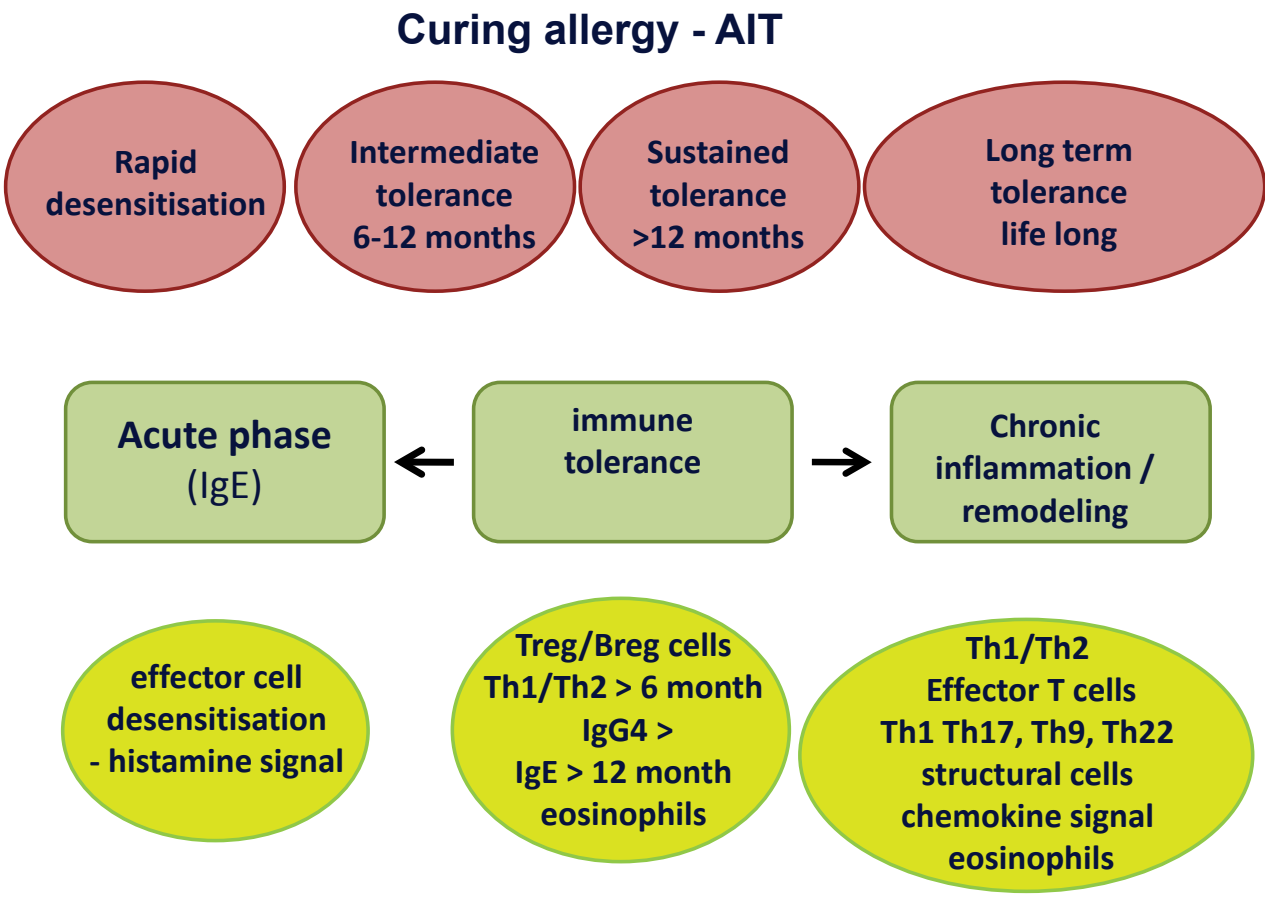

Figure 2 AIT triggers multiple mechanisms, which are sequentially activated. These events lead to multifaceted clinical improvement. Rapid desensitization to allergen, long-term allergen-specific immune tolerance as well as the suppression of allergic inflammation appears. AIT – allergen immunotherapy; Breg = B regulatory cell; Th = T helper cell; T reg = T regulatory cell.

8b SUBCUTANEOUS ALLERGEN IMMUNOTHERAPY FOR ALLERGIC RHINITIS

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Allergic rhinitis (AR) is common and often poorly controlled by standard drug therapy. In subcutaneous allergen immunotherapy (SCIT) patients receive a course of injections of allergen extracts, which desensitize them, reducing symptoms and medication requirements. The dose is built up over 7-12 weekly injections; if maintenance injections are required these are given every 4-6 weeks for about 3 years.

KEY MESSAGES

- Subcutaneous allergen immunotherapy (SCIT) is effective for seasonal and perennial allergic rhinitis
- Clinical effectiveness requires several years of treatment
- SCIT modifies the course of allergic disease, evidenced by reduced rates of new allergic sensitizations and prevention of progression from rhinitis to asthma
- The clinical effect of SCIT persists for years after it is discontinued

CLINICAL EFFICACY

The value of SCIT for seasonal AR has been confirmed in many randomized placebo-controlled trials. Improvement is expected in about 80% of patients; symptoms are reduced rather than abolished, with a marked reduction in the number of days with very bad symptoms compared to untreated or placebo-treated controls.

In patients with perennial AR, it can be difficult to work out how much of their symptoms are due to allergy. SCIT with HDM extracts can be effective in controlling symptoms of perennial AR but patient selection is critical. If there is no benefit after 6 months, SCIT is unlikely to be effective and alternative strategies should be considered. SCIT can be used in cat allergy but is usually restricted to people with occupational exposure. There is no corresponding data for dog allergy.

EVIDENCE OF DISEASE MODIFICATION

SCIT may have long term benefits by modifying the course of the disease, whereas drug therapies only suppress the symptoms while they are taken. Two outcomes offer evidence of disease modification – the prevention of asthma in patients treated for AR and the prevention of new allergic sensitisations (Figure 1). After cessation of SCIT treatment, there is a slow recurrence of symptoms over the first 3 years after completing SCIT, but no appreciable increase thereafter.

ADVERSE REACTIONS TO SCIT

Localized and systemic reactions may occur after SCIT. Local reactions are commoner during the build-up phase than during maintenance, but do not predict subsequent occurrence of systemic reactions. Systemic reactions are more serious and can very rarely prove fatal. Consequently, SCIT injections should only be given in clinics familiar with SCIT and by clinicians able to deal with anaphylactic side-effects.

FUTURE DIRECTIONS

Given the time, cost and risks of conventional SCIT, there is interest in modifications that may increase efficacy, simplify the regime or improve safety (Table 1).

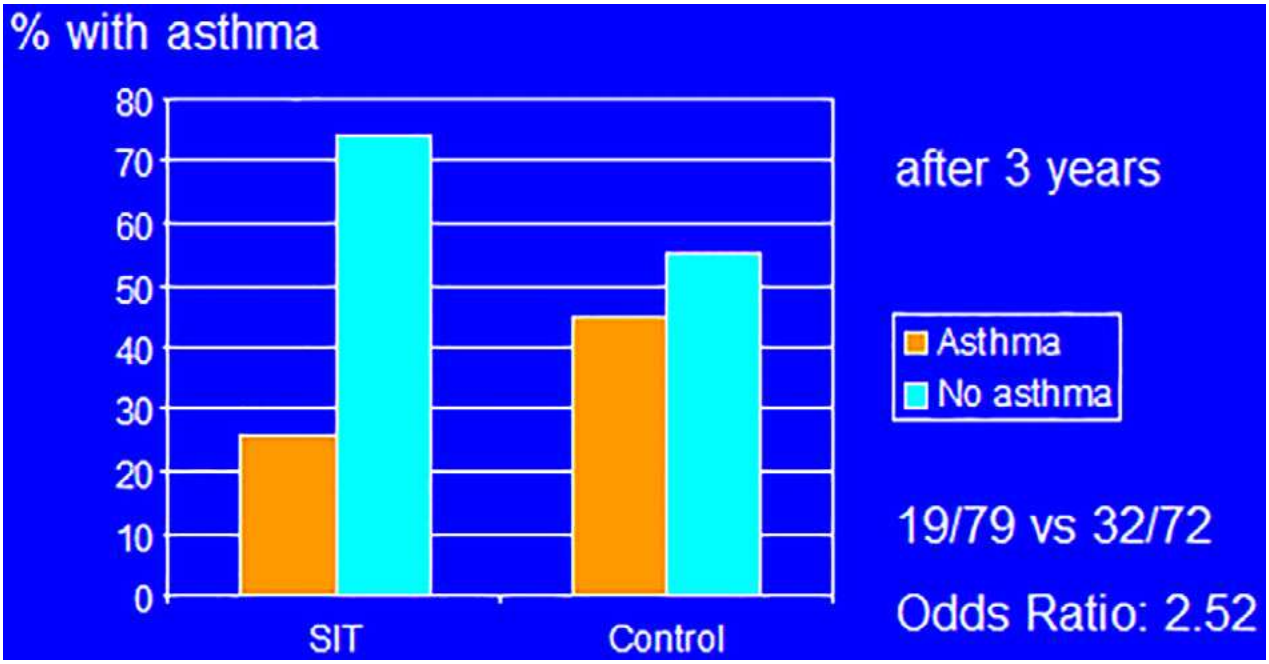

Figure 1 Pollen SCIT reduces asthma in children with seasonal rhinitis. (*Reprinted from J Allergy Clin Immunol, 109/2, Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study), 251-256, Copyright 2002, with permission from Elsevier.*)

TABLE 1

Future developments
modified natural allergens
recombinant allergens
modified recombinant allergens (hypoallergenic variants)
immunological adjuvants (CpG-DNA; LPS derivatives)
alternative routes of administration (Sublingual, intralymphatic, liposomes etc).

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8c SUBLINGUAL IMMUNOTHERAPY FOR ALLERGIC RHINITIS

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KEY MESSAGES

- Sublingual allergen immunotherapy (SLIT) is currently considered an alternative treatment to the subcutaneous route and has been included in international guidelines for the treatment of allergic rhinitis (AR)
- SLIT significantly reduces symptoms scores and the use of rescue medication in both adults and children with AR
- A disease modification effect was proved 2 years after the completion of 3 years of treatment with SLIT-tablets for grass pollen allergy
- The safety profile of SLIT is extremely good; therefore, SLIT can be self-administrated by the patients in their homes

Sublingual allergen immunotherapy (SLIT) is currently considered an alternative treatment to the subcutaneous route. The use of SLIT has been included in international guidelines for the treatment of allergic rhinitis (AR) with or without conjunctivitis. SLIT can be administered as drops or tablets for respiratory allergies due to grass, tree, ragweed pollens and house dust mites. At present, SLIT is commercialised and routinely used in some countries in Europe (e.g., France and Italy) and is becoming popular in many other countries around the world. Some SLIT products have also been recently approved by the FDA in the USA.

CLINICAL EFFICACY

The clinical efficacy of SLIT is well documented in different double-blind, placebo-controlled, randomised clinical trials (DBPC RCTs) and meta-analyses (Tables 1 and 2). SLIT significantly reduces symptoms scores and the use of rescue medication in both adults and children. Large clinical and methodological heterogeneity was detected in these analyses. New well-powered well-designed multinational DBPC RCTs using almost comparable clinical outcomes and properly standardised sublingual products have demonstrated sustained clinical efficacy in the active group relative to placebo. These studies have also indicated a disease modification effect observed 2 years after the completion of 3 years of treatment with SLIT-tablets for grass pollen allergy.

SAFETY

The safety profile of SLIT is extremely good; therefore, SLIT can be self-administrated by the patients in their homes. However, it is recommended that the first dose should always be given to the patient in the presence of a physician. This is to re-assure the patient about the expected local symptoms he/she can experience while taking the medication. Most reported symptoms are self-limited, mild in severity and do not require any other relief medication. Local symptoms are itching/tingling of the lips, mouth or/and oral mucosa; mild local swelling of lips, sublingual area or tongue. Very rarely, systemic reactions appear. Few so-called anaphylactic cases have been globally reported. No fatalities are related to SLIT. Good adherence to SLIT is critical for its success, at least 3-4 visits per year should be programmed to evaluate adherence and clinical response to SLIT.

TABLE 1

The clinical efficacy of SLIT – decrease in symptom scores

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I^2†
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon, 2007	15	Adults	597	466	-0.73 (-0.97 to -0.50)	63%
Asthma	Abramson, 2010	34	Adults and children	727	557	-0.59 (-0.83 to -0.35)	73%
SLIT							
Rhinitis	Wilson, 2003	21	Adults and children	484	475	-0.42 (-0.69 to -0.15)	73%
Rhinitis	Penagos, 2006	10	Children	245	239	-0.56 (-1.01 to -0.10)	81%
Rhinitis	Radulovic, 2011	49	Adults and children	2333	2256	-0.49 (-0.64 to -0.34)	81%
Asthma	Calamita, 2006	9	Adults and children	150	153	-0.38 (-0.79 to 0.03)	64%
Asthma	Penagos, 2008	9	Children	232	209	-1.14 (-2.10 to -0.18)	94%
Conjunctivitis	Calderon, 2011	36	Adults and children	1725	1674	-0.41 (-0.53 to -0.28)	59%
House dust mites	Compalati, 2009	8	Adults and children	194	188	-0.95 (-1.77 to -0.14)	92%
Grass allergens	Di Bona, 2010	19	Adults and children	1518	1453	-0.32 (-0.44 to -0.21)	56%

**Effect size (SMD): poor, <20.20; medium, 20.50; high, >20.80.*

†Heterogeneity (I2) 5 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity

TABLE 2

The clinical efficacy of SLIT – decrease in medication

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I^2†
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon, 2007	13	Adults	549	414	-0.57 (-0.82 to -0.33)	64%
Asthma	Abramson, 2010	20	Adults and children	485	384	-0.53 (-0.80 to -0.27)	67%
SLIT							
Rhinitis	Wilson, 2003	17	Adults and children	405	398	-0.43 (-0.63 to -0.23)	44%
Rhinitis	Penagos, 2006	7	Children	141	138	-0.76 (-1.46 to -0.06)	86%
Rhinitis	Radulovic, 2011	38	Adults and children	1737	1642	-0.32 (-0.43 to -0.21)	50%
Asthma	Calamita, 2006	6	Adults and children	132	122	-0.91 (-1.94 to 0.12)	92%
Asthma	Penagos, 2008	7	Children	192	174	-1.63 (-2.83 to -0.44)	95%
Conjunctivitis	Calderon, 2011	13	Adults and children	560	478	-0.10 (-0.22 to 0.03)	34%
House dust mites	Compalati, 2009	4	Adults and children	89	86	-1.88 (-3.65 to -0.12)	95%
Grass allergens	Di Bona, 2010	17	Adults and children	1428	1358	-0.33 (-0.50 to -0.16)	78%

**Effect size (SMD): poor, <20.20; medium, 20.50; high, >20.80.*

†Heterogeneity (I2) 5 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.

MECHANISMS

The mechanisms of SLIT are less well understood than those of subcutaneous immunotherapy. SLIT products should be placed under the tongue, allowing the allergen to be in contact for at least 2 minutes with the oral mucosa through dendritic cells. The allergens cross the mucosa in 15 - 30 minutes. They are then captured by tolerogenic dendritic cells and processed as small peptides. Then, via the lymphatic system a systemic immune response is created, aiming to produce an early decrease in mast cell and basophil degranulation. This is followed by generation of allergen-specific Treg cells and suppression of allergen-specific Th1 and Th2 cells and possibly other effector cells. An early increase and a very late decrease in specific IgE levels are observed. IgG4 levels show a relatively early increase that is dose dependent. A significant decrease in the allergen-specific IgE/ IgG4 ratio occurs after several months.

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8d NEW VACCINES FOR ALLERGEN IMMUNOTHERAPY

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KEY MESSAGES

- A short, safe and effective intradermal injection regimen that confers long-lasting clinical benefit would be an appealing alternative to current AIT which necessitates a prolonged 3-5 year treatment regimen
- Synthetic peptide immuno-regulatory epitopes (SPIREs) represent a new class of therapeutics for allergen immunotherapy (AIT) that afford the potential to suppress the IgE-mediated allergic cascade through induction of T-cell tolerance
- Dose-ranging and safety studies, cat allergen provocation studies, and environmental exposure chamber studies have demonstrated a therapeutic effect for cat, ragweed, grass, and house dust mite synthetic peptide constructs
- Several novel approaches such as B cell epitopes combined with Pre S antigen of hepatitis B virus, modular allergen-translocating vaccines, combined recombinant allergens are underway

The focus of specific allergen immunotherapy (AIT) is to effectively control the allergic cascade and thereby suppress the allergic inflammatory response and attenuate, if not completely abrogate, the clinical symptomatology that otherwise manifests as allergic rhinoconjunctivitis and/or asthma.

The ability to prevent the allerrgic immune response is a primary goal of AIT, and new advances in immunotherapeutics directed at inducing T-cell tolerance, shifting the balance in Th2 vs Th1 cellular subtypes, or upregulating T-regulatory cells are at the stage of promising Phase 2-3 clinical development.

T-CELL-TOLERIZING PEPTIDES

A therapeutic approach in AIT uses T-cell-tolerizing peptides to induce immune tolerance and thereby suppress IgE-mediated diseases. Early work in this research area was carried out by Gefter and colleagues in the mid-1990s, and these studies provided the first evidence that synthetic T-cell-tolerising peptides could induce tolerance and thereby open a treatment pathway to suppress IgE-mediated allergic diseases such as cat and ragweed-induced rhinitis and asthma. Gefter's lab developed both cat (two 27 amino acid peptides derived from *Fel d 1*) and ragweed (derived from *Amb a 1*), T-cell-tolerizing peptides, and in collaborative work with Norman and Creticos, demonstrated that administration of these peptides, in various subcutaneous treatment regimens, resulted in significant improvement in cat-induced clinical symptoms in studies utilizing cat broncho-provocation or natural cat room challenges and in multicenter field trials of the ragweed vaccine.

However, these first-generation peptides were not optimal when compared to conventional AIT, as they were longer sequenced peptides (potentially exposing IgE epitopes), too few in number (hence, not providing a more complete immune protection), and required administration of higher subcutaneous doses which were associated with late-onset adverse events.

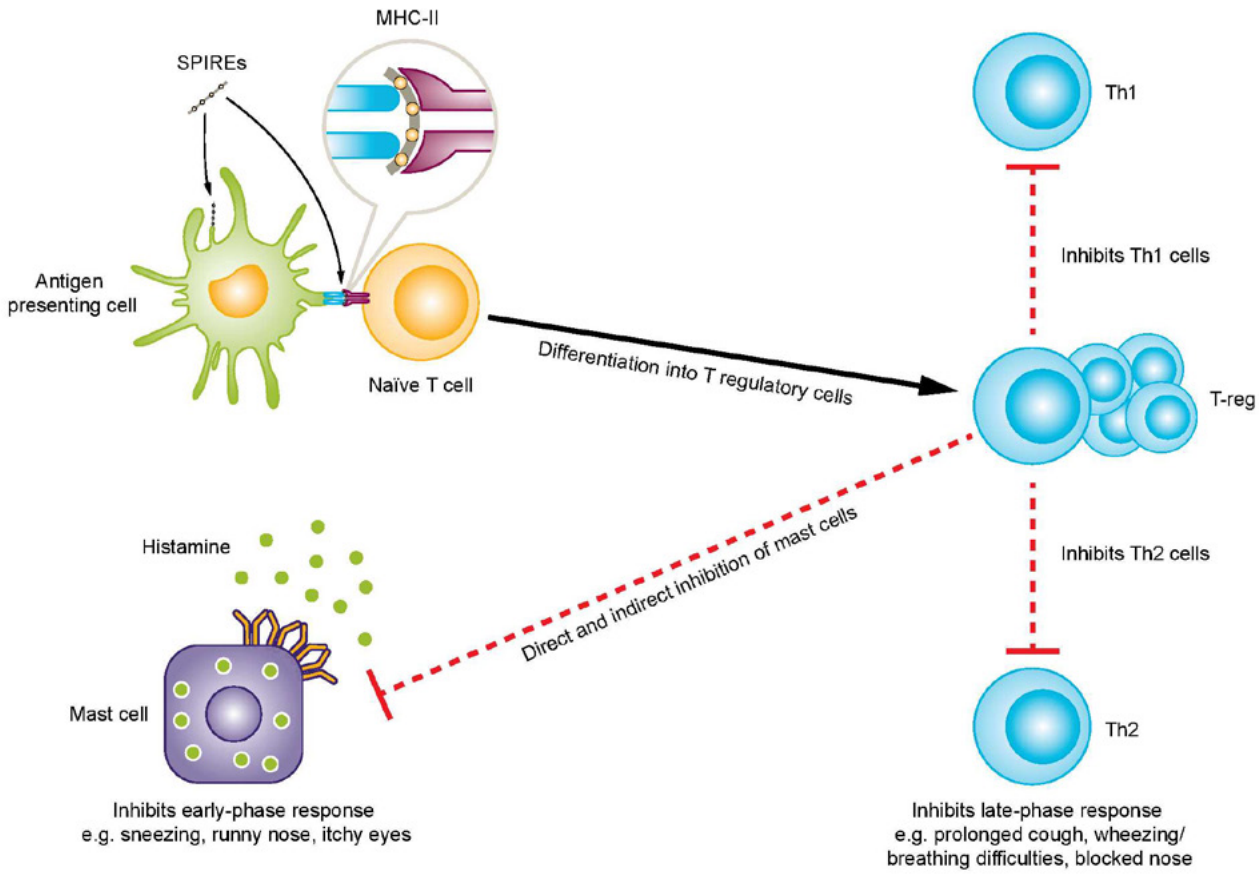

Figure 1 Mechanistic schematic representation of synthetic peptide immune-regulatory epitopes. (*This figure reproduced with permission from: BioMed Central; published in: Creticos PS. Advances in synthetic peptide immune-regulatory epitopes. World Allergy Organ J 2014; 7:30.*)

SYNTHETIC PEPTIDE IMMUNO-REGULATORY EPITOPES

New research into peptide epitopes initiated at Imperial College by Mark Larché and Barry Kay has resulted in the development of a second generation of these molecules - Synthetic Peptide Immuno-Regulatory Epitopes (SPIREs). These synthetic T-cell-tolerizing peptides are comprised of smaller peptide units (e.g.: cat: seven peptides; 13-17 amino acids in length), administered in much smaller quantities (75 µg vs. 750 µg), assembled from different T-cell epitopes, and administered intradermally to more efficiently access antigen-presenting cells.

These novel peptides are specifically designed to induce immunologic tolerance through binding to MHC class II molecules on antigen-presenting cells, with subsequent up-regulation of regulatory T-cells (Figure 1). A key advantage of these peptides lies in their smaller size; i.e., molecules that are of insufficient length to trigger cross-linking of IgE on mast cells and basophils, thus significantly reducing the risk of IgE-mediated allergic reactions (e.g., asthma, angioedema/urticaria, or anaphylaxis).

MECHANISTIC STUDIES

The leading SPIRE construct is the cat peptide derived from Fel d 1, the major cat allergenic moiety. Mechanistic studies with these peptides in mice have demonstrated reduction in BAL total cells and eosinophils, pulmonary and systemic Th-2 inflammatory cytokines, recruitment of Th-2 cells to the lungs, and of prolif-

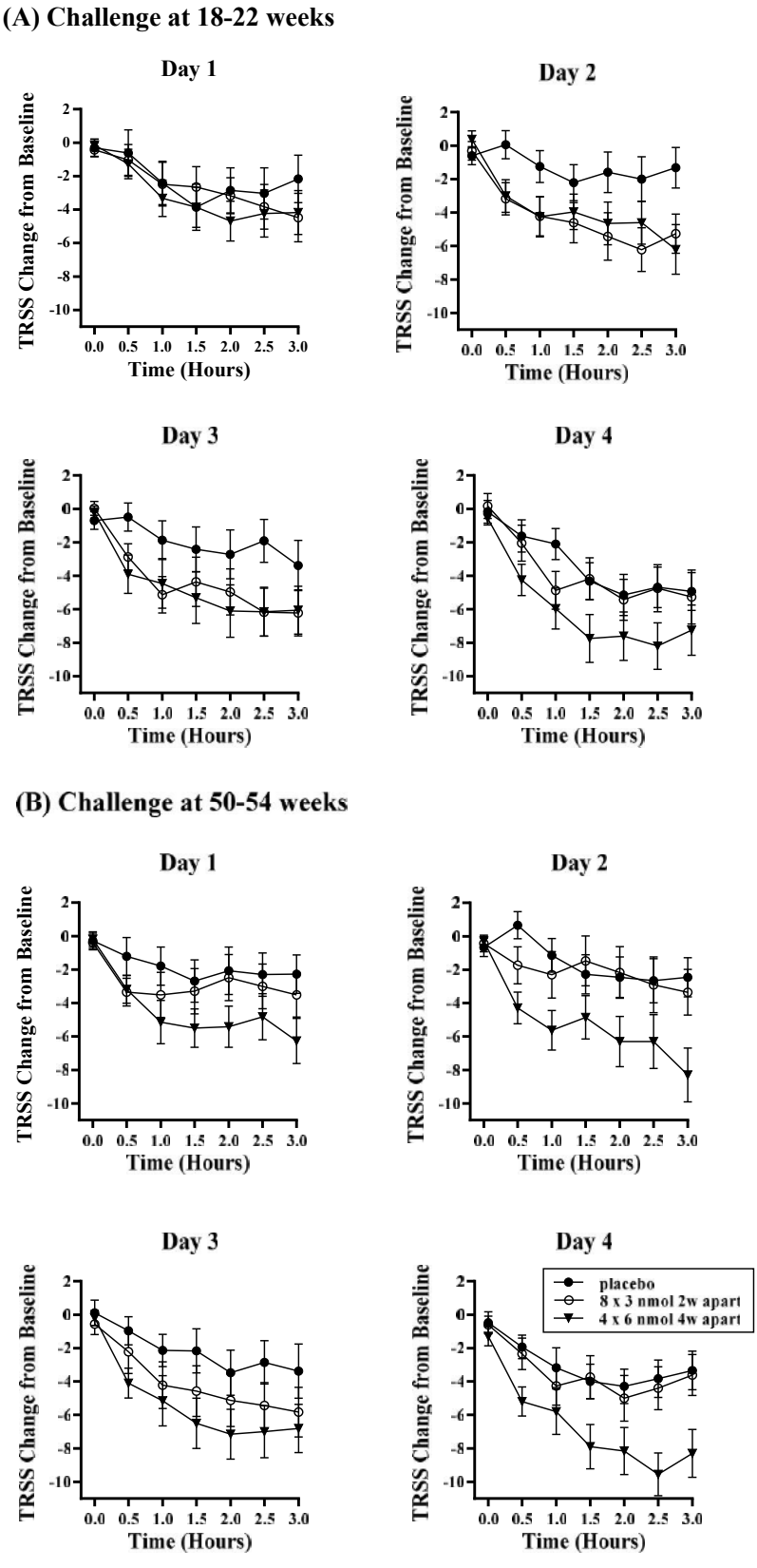

Figure 2 Delta changes in total rhinoconjunctivitis symptom scores for the treatment effect observed with Cat-SPIRE in the environmental exposure chamber. In this DBPC study, 202 cat-allergic subjects were randomized to either: a) 4 doses of 6-nmol 4 weeks apart (n=66); b) 8 administrations of 3 nmol 2 weeks apart (n=67); or c) placebo (n=69). Subjects underwent a baseline challenge (4 consecutive days of 3 hours in the EEC) and patients returned for the identical challenge protocol in the EEC at 18-22 weeks and at 50-54 weeks after the start of treatment. The primary endpoint was defined as the change in TRSS, (post-treatment vs. baseline EEC challenges) at 1-3 hours on days 2-4. The results of this 1-year study demonstrated a persistent treatment effect in the pre-specified statistical analysis at time points after 1 hour on Days 2-4 of EEC at the 50-54 week EEC challenge in the non-asthmatic population for the 6 nmol x 4 dose regimen vs. placebo [median change: -6.80 (vs. -3.27); mean change: -3.89 +/-5.56 (vs. -2.91 +/-5.56); LS means: -7.074, -4.077; 95% CIs: -7.165 to -0.989; p value =0.0104]. Analysis of the data at all time-points, on all days, showed similar results. The challenge performed at 1-year demonstrated the treatment effect was observed to be stronger on successive days in the EEC.

erative responses to Fel d 1. Furthermore, evidence for the role of IL-10 in the underlying mechanism of action is provided by the observation that administration of anti-IL-10 monoclonal antibody, immediately post-treatment with the peptide, blocked the positive peptide-inducing effects. Subsequently, initial safety and efficacy work was published which defined the optimal peptide construct and the applicability of a short intradermal injection regimen.

SALIENT CLINICAL STUDIES

Utilizing a controlled cat allergen environmental exposure chamber (EEC) model, dose-ranging and dose-dependent clinical efficacy and safety studies have demonstrated that a long-lasting persistence of effect [i.e., improvement in total rhinitis clinical symptoms (TRSS)] can be demonstrated as far out as 1-year after completion of a concise injection regimen (6 nmol x 4 ID injs x 4 wks apart) (Figure 2). A subgroup of subjects followed for 2 years has now shown a similar magnitude of effect upon chamber exposure. The magnitude of change in TRSS scores in the EEC model (~4 TRSS units vs placebo) compares favorably with chamber studies performed with cat SCIT (3u), cat SLIT-drops (1.6u), or an antihistamine (1.3u). Furthermore, the evidence for a long-lasting effect parallels that observed with SCIT and SLIT in which 3-year courses of treatment are necessitated to obtain a sustained treatment effect in the 2-years post-cessation of treatment.

A large Phase 3 multicenter randomized DBPC clinical field trial is currently underway with the cat construct, and the findings from this trial should further elucidate the potential for this novel immunotherapeutic in the treatment of cat allergy. In addition, the SPIRE platform has further branched into ragweed, grass, and house dust mite development programs.

CONCLUSION

Synthetic peptides comprised of T-cell epitopes, derived from known amino acid sequences of specific relevant allergens, afford a unique opportunity through a short intradermal injection regimen to safely and effectively induce immunologic tolerance and hence initiate long-lasting clinical efficacy.

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8e AIT FOR ALLERGIC RHINITIS - NEW DELIVERY OPTIONS

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KEY MESSAGES

- Allergen immunotherapy (AIT) works by stimulating DCs, T- and B-cells. In contrast, side effects are mediated by mast cells and via blood vessels
- The ideal route for AIT is characterized by high density of DCs, T- and B-cells, but low density of mast cells and blood vessels
- Lymph nodes contain masses of DCs, T- and B-cells, but few mast cells. Intralymphatic AIT (ILIT) was safe and the number of allergen injections cold be reduced to three
- The epidermis contains dense DCs and no mast cells or blood vessels. Epicutaneous AIT (EPIT) was safe and the allergen administrations could be reduced to 6 patches

For allergic rhinitis (AR) allergen specific immunotherapy (AIT) is the only causal treatment with long-term efficacy that in addition prevents progression to asthma. Current AIT suffers from two short-comings. First, allergen administration causes allergic adverse effects. Local adverse effects are mediated by mast cells at the site of allergen administration, whereas systemic adverse effects occur when allergen reaches blood vessels and activates basophils or gets distributed systemically to tissue resident mast cells (Figure 1). The second short coming is that current AIT requires numerous allergen administrations over three to five years and thus is time consuming. Due to these two disadvantages few allergic patients opt to undergo AIT and treatment adherence is poor.

HOW TO IMPROVE SAFETY?

Local and systemic allergic side effects can be prevented by reducing the IgE binding capacity of the therapeutic allergen, either by chemical or recombinant modification, or by use of oligopeptides representing merely T cell epitopes. Another strategy to reduce local side effects is choosing a route of allergen delivery, which is characterized by low density or absence of mast cells. Also, systemic side effects should be preventable, when choosing a route characterized by low density or absence of blood vessels, minimizing risk for systemic allergen distribution.

HOW TO REDUCE THE NUMBER OF ALLERGEN ADMINISTRATIONS?

The number of allergen administrations can be reduced by enhancing the immunological effects of each administration. AIT works by inducing blocking antibodies, T helper 1- and regulatory T cells, orchestrated by dendritic cells (DCs). Immunological effects are classically enhanced by adjuvants. Replacing alum by bacterial products such the lipopolysaccharides derivative monophosphoryl lipid A (MPLA) or bacterial DNA allows reducing the number of injections to 4 or 6. Another strategy is choosing an administration route which is characterized by high density of DCs, B- and T-cells.

INTRALYMPHATIC IMMUNOTHERAPY (ILIT)

In lymph nodes, the density of DCs, B- and T-cells is maximal, whereas the density of mast cells is low. We could demonstrate that direct injection of allergen into a

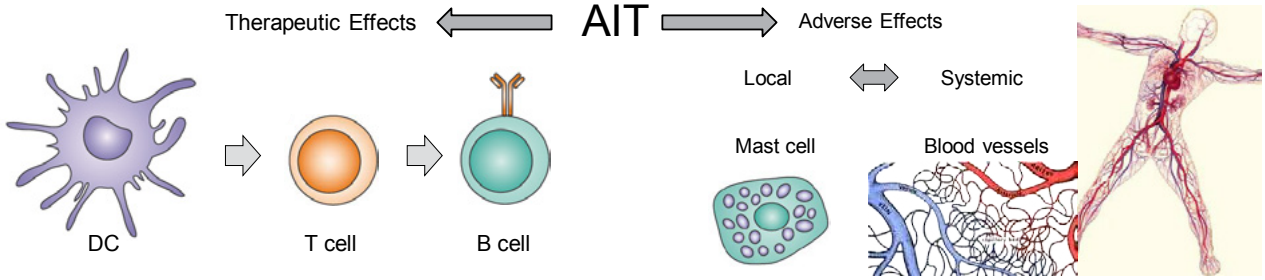

Figure 1 Cells mediating the therapeutic effect of AIT vs. cells mediating adverse effects. While the therapeutic effects of AIT are mediated by DCs, T-cells and B-cells, the local adverse effects are mediated by mast cells at the site of injection and the systemic adverse effects are mediated when allergen accidentally reaches the blood circulation so that it can activate basophils and/or tissue resident mast cells. Therefore the ideal route for allergen administration should be characterized by a high density of DCs, T- and B-cells, but a low density of mast cells and blood vessels.

subcutaneous lymph node was safe and ameliorated symptoms of AR already after three injections.

EPICUTANEOUS IMMUNOTHERAPY (EPIT)

The epidermis is characterized by high density of potent DCs and absence of blood vessels. AIT administered via this route should therefore be more efficient and safer. In fact, we could demonstrate that EPIT was safe and ameliorated symptoms of AR already after 6 allergen patch applications

The above mentioned two promising allergen delivery routes have been clinically developed by us and others.

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8f REGULATION AND STANDARDIZATION OF AIT EXTRACTS

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KEY MESSAGES

- Allergenic products for allergen immunotherapy (AIT) are biologics that require a marketing authorization (MA) in the EU and the US
- The regulatory process consists of scientific advice, review, and regulation of clinical trials and the MA procedure;
- Authorization is granted on the basis of quality, safety and efficacy, and a benefit-risk assessment; the regulatory process continues after authorization and may include additional clinical trials
- The quality of natural allergen extracts depends on the source material and the production process and is difficult to standardize
- Standardization is based on FDA standards in the US and on In House References in the EU
- For many products, potency of standardized extracts is still based on allergen binding by IgE antibodies from allergic subjects
- Novel approaches to allergenic product testing include purified recombinant allergens as international reference standards, sandwich ELISAs for major allergen quantification, and mass spectrometry

Licensed allergen products for allergen immunotherapy (AIT) are extracts derived from biological source materials such as pollen or house dust mites. They are biomedicines requiring a marketing authorization both in the EU and the US. The quality and consistency of biomedicines strongly depends on the standardization of the production process. Moreover, due to natural biovariability of the composition of source materials, AIT extracts are difficult to standardize.

In the US, clinical development begins with an investigational new drug (IND) application. While not mandatory, US Food and Drug Administration (FDA) encourages a Pre-IND meeting, for which supporting documentation includes the investigational plan and an outline of chemistry, manufacturing and control (CMC) information. The subsequent IND application includes a Phase 1 protocol to support safety. Phase 2 studies determine proper dosing range and support efficacy, after which the sponsor is encouraged to request an End of Phase 2 (EOP2) meeting to discuss criteria for successful Phase 3 studies. Within 60 days of the EOP2 meeting a sponsor should submit their initial pediatric study plan (iPSP). The iPSP must include plans for pediatric studies, and any plans to request waivers or deferrals of the requirement to submit data to support use of the product in pediatric populations at the time of submission of a biologics license application. Phase 3 protocols should include comprehensive CMC information and (ideally) a Statistical Analysis Plan. The product used for Phase 3 studies should be manufactured in the same facilities and using the same process intended for the licensed product. After completion of Phase 3, the sponsor is encouraged to request a pre-BLA meeting to discuss the proposed content of a BLA, which should

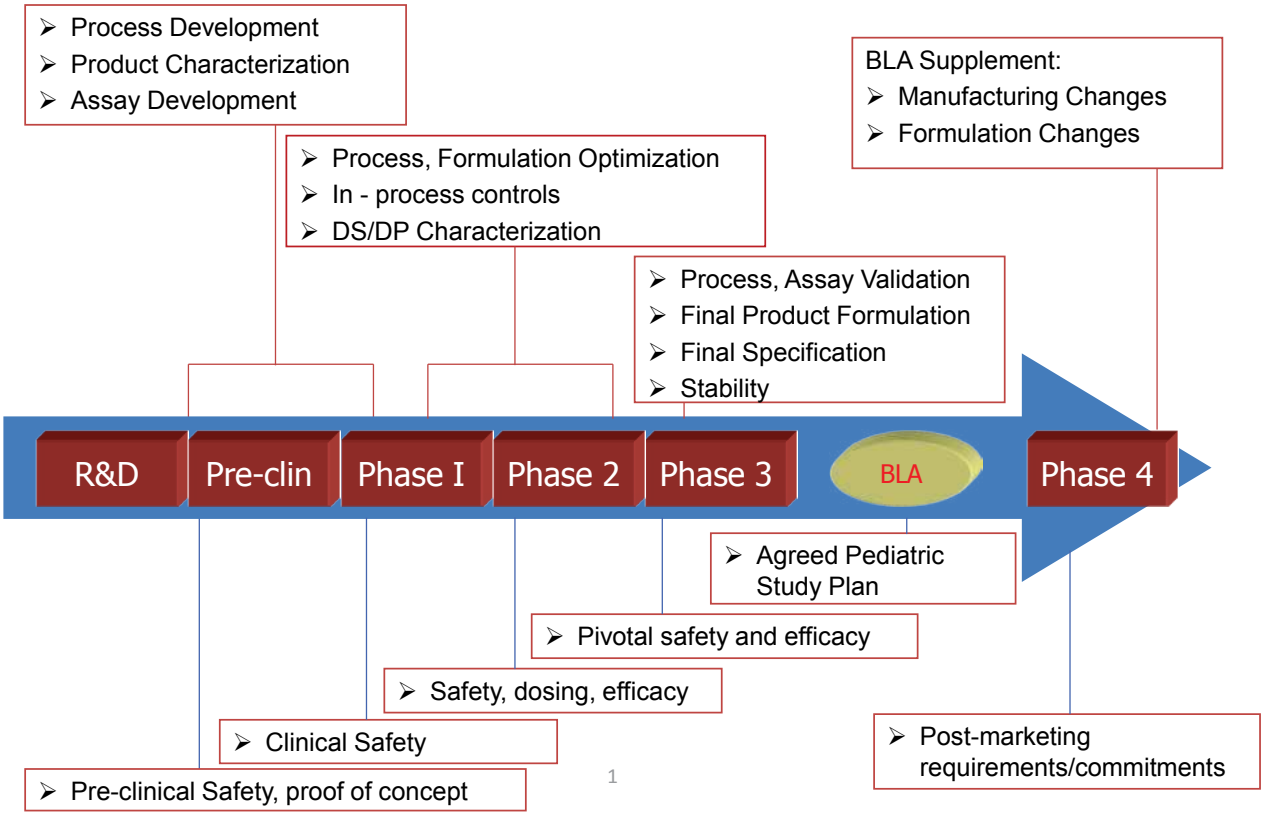

Figure 1 Steps in the development of an allergenic vaccine following the rules of an investigational new drug in the US.

include an agreed upon PSP. After approval of a BLA, the manufacturer is authorized to market a product for interstate commerce in the US (Figure 1).

In the EU allergen extracts are authorized at the level of individual member states (MS). Once a product is authorized in one MS the license can be extended to other MS by a mutual recognition procedure. Moreover, the decentralized procedure, in which one MS acts as reference member state (RMS) allows to simultaneously obtain a marketing authorization in two to all MS. The system of clinical testing is similar to the US, and medical agencies offer scientific advice to pharmaceutical companies and other sponsors (similar to Pre-IND meetings). Approval of a pediatric investigation plan by the European Medicines Agency is required before an authorization of the products for use in adults can be granted (Figure 2).

In the EU, biological allergen standardisation is mainly based on skin testing during development of a new product and on IgE inhibition tests comparing a given extract batch with a reference preparation for evaluating batch to batch consistency. In the US, FDA allergen standards and allergic human reference sera are used, while the system in the EU is based on In House Reference Preparations (extracts) and human sera pools that are manufacturer specific. Recent progress in allergen standardisation are the development and validation of purified recombinant allergen standards and the use of sandwich ELISA systems for determination of individual allergens in extracts, as well as proteomic tools such as mass spectrometry.

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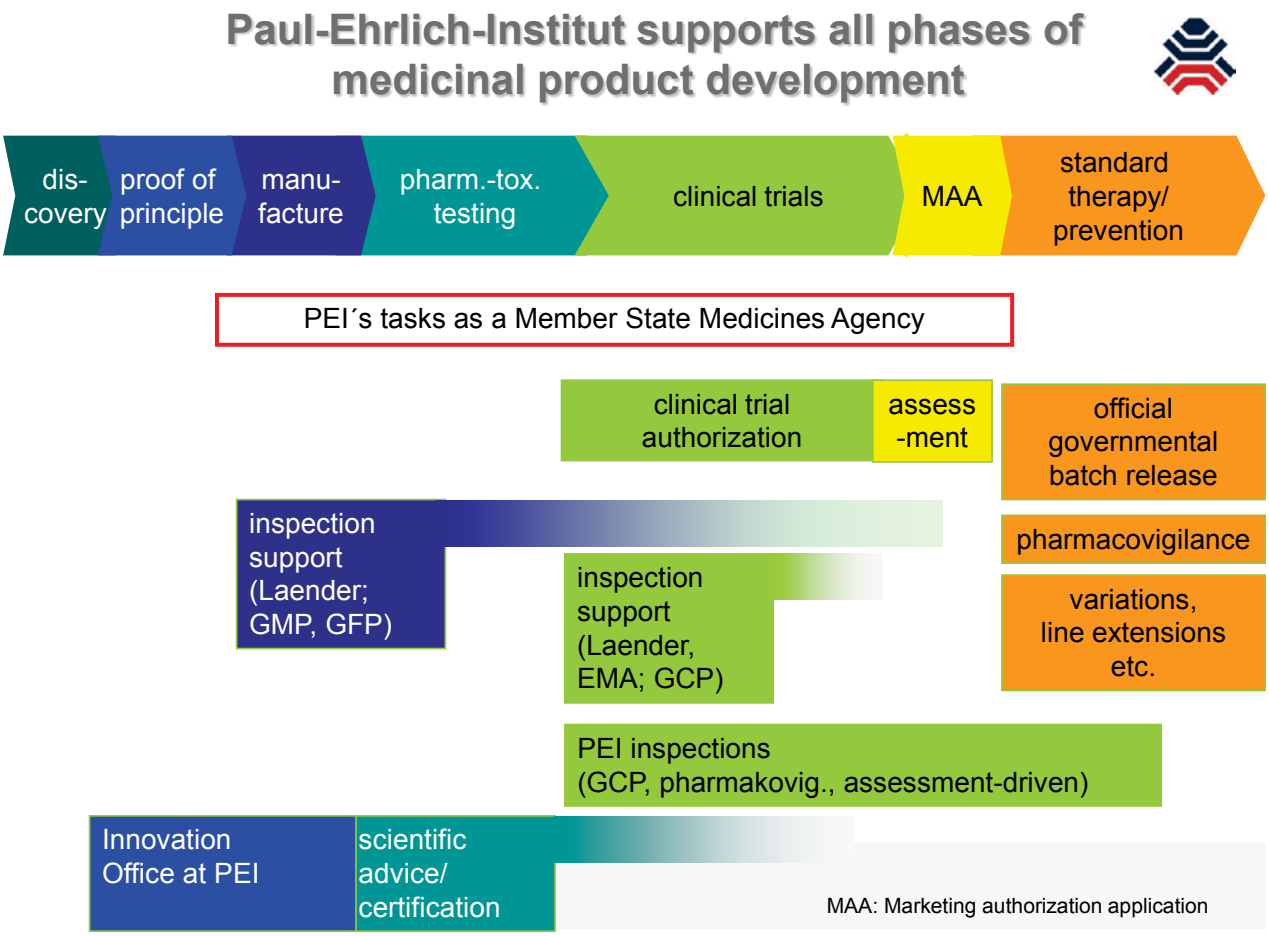

Figure 2 Steps in the development of an allergenic vaccine following the rules of an investigational new drug in the EU.

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9 TREATMENT OF ALLERGIC RHINITIS WITH BIOLOGICALS AND MONOCLONAL ANTIBODIES

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KEY MESSAGES

- Treatment with anti IgE-Antibodies is effective in providing symptom control of allergic rhinitis (AR) in an allergen-nonspecific fashion
- In contrast to allergen-specific immunotherapy treatment of AR with anti-IgE is probably not disease modifying
- As a proof of concept, other biologicals (antibodies anti IL5, IL4 or IL13) should be studied in AR

Since allergic rhinitis (AR) is probably the most classical IgE mediated part of all atopic manifestations, it is quite tempting to utilize the recently developed pathogenesis oriented interventions as "a proof of concept" in this disease. However, most of the modern tools are currently studied and will probably be marketed only for asthma for non-scientific but mainly economic reasons: disease related costs as well as impairment for the quality of life in patients suffering from asthma is much more relevant compared to AR which is by many physicians and health care providers still considered trivial, transient and relatively "cheap" disease.

Studies have indicated, however, that around 50 % of the patients affected have to be categorized as persistent AR with severe impairment which means that the daily life of the affected patients in school or work is markedly affected. Still the aspect of cost effectiveness with modern antiallergic biologicals and monoclonal antibodies will be discussed not only within the scientific society but also by health of authorities and payers.

So far in most countries patients with AR are treated according to international or national guidelines, primarily with modern antihistamines (oral or topical) and topical corticosteroids. The treatment effect of this pharmacotherapeutic approach is well documented, but not really impressive. Allergen immunotherapy (AIT) is applied by the subcutaneous or sublingual route. It can be assumed that the AIT disease modifying effect is stronger than drug treatments, although head-to-head comparisons are not really available for final and conclusive judgments.

Since anti-IgE has become available, a number of studies have been performed in seasonal AR. anti-IgE was applied either alone or together with AIT (Figure 1). A recent metaanalysis concludes that in seasonal and perenial AR treatment with Omalizumab provides an improvement of daily nasal symptoms severity score or reduction of anti-allergic medication, compared with placebo. Looking at the different trials it is obvious, that not all of these studies are adequately powered so that larger clinical trials and economic studies are still needed to address the issues of rare adverse events occurrence or cost effectiveness respectively. So far one can conclude that Omalizumab as the only biological which has so far been investigated in AR is significantly associated with symptom relief, decreased rescue medication use and improve quality of life in patients with inadequately controlled AR or rhinosinusitis refractory to conventional treatment. The more recently de-

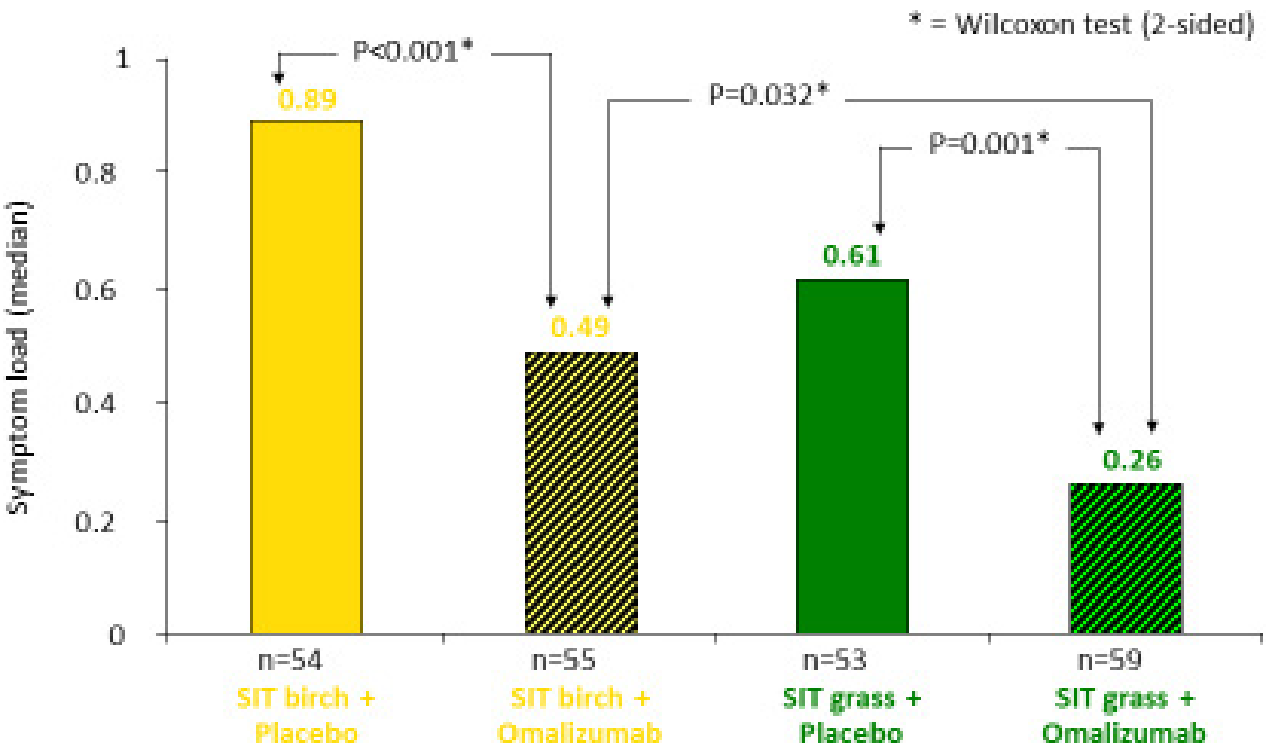

Figure 1 Treatment of polyallergic (birch and grass pollen) children with allergic rhinitis. Effect of intervention with allergen immunotherapy (either birch or grass pollen) or Omalizumab documented during the grass pollen season. (*Reprinted from J Allergy Clin Immunol, 109/2, Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, Leupold W, Bergmann KC, Rolinck-Werninghaus C, Gräve M, Hultsch T, Wahn U. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis, 274-280, Copyright 2002, with permission from Elsevier.*)

veloped biologicals like anti-IL5, combined antibodies to IL4 and IL 13 or their receptor have so far only been used for asthma trials.

Given the fact that in atopic diseases, particularly in children and adolescents, the majority of patients develop IgE-mediated comorbidities in the lower airways, the skin or the gastrointestinal tract, it is mandatory, that future pathogenesis oriented systemic intervention will also carefully assess the effect of the treatment with biologicals on AR. In addition AR patients with a broad spectrum of relevant seasonal or perennial allergies may benefit better from a nonspecific antiallergic approach using monoclonal antibodies, if they are not sufficiently controlled by standard treatment, rather though AIT.

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10 OTHER TARGETED TREATMENT OPTIONS FOR ALLERGIC RHINITIS

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Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated disease, whereby inhaled allergens cause a type 1 hypersensitivity reaction. Inflammation in AR is driven by a variety of cell types including mast cell activation, the infiltration of sensitized tissues by eosinophils and T helper type 2 (Th2) lymphocytes. Recent advances in the understanding of new pathways and factors involved in allergic diseases suggest new therapeutic avenues for the treatment of AR.

Toll-like receptors (TLR) belong to a large family of pattern recognition receptors known as the ancient 'gatekeepers' of the immune system. TLRs are located at the first line of defense against invading pathogens (bacteria and viruses) as well as aeroallergens. They can modulate the Th2 specific allergic immune response towards a Th1 response, which make them appropriate adjuvants for allergy vaccines, as well as as stand-alone therapeutics to treat symptoms of AR patients. Using oligonucleotides enriched in CpG motifs as a TLR-9 agonist or other TLR agonist against like TLR-4, TLR-7 and TLR-8 have been successfully investigated in early clinical trials in AR (Table 1).

KEY MESSAGES

- Recent advances in the understanding of new pathways and factors involved in allergic diseases suggest new therapeutic avenues for the treatment of allergic rhinitis
- Toll like receptor agonists, which mimic the beneficial modulation of viruses and bacteria on the allergic inflammation
- CRTH2 (or DP2) receptor antagonists, which block the effects of the mast cell derived mediator prostaglandin D2
- MicroRNA inhibitors which might posttranscriptionally regulate key pathogenetic mechanisms in allergic inflammation

Prostaglandin D2 (PGD2), an arachidonic acid metabolite, is a key mediator in inflammation after allergen exposure and is released by IgE-activated mast cells and by other inflammatory cell types. PGD2 helps in recruiting and activating Th2 lymphocytes, eosinophils and basophils (Figure 1). Nasal challenge with PGD2 induces a greater degree of nasal congestion than that induced by histamine. The proinflammatory effects of PGD2 occur through interactions with the chemoattractant receptor homologous molecule on Th2 cells (CRTH2), a 7-transmembrane type G protein–coupled receptor selectively expressed on Th2 cells, T cytotoxic type 2 cells, eosinophils, and basophils (Figure 1). Around 20 CRTH2 (or DP2 receptor) antagonists have been developed into clinical development with different effectivity for systemic treatment of AR. A reduction in nasal allergic symptoms as well as in local nasal biomarkers has been shown in patients with AR exposed to grass pollen.

MicroRNAs (miRNAs) are a class of short single stranded RNA molecules that posttranscriptionally silence gene expression and have been shown to fine-tune gene transcriptional networks. Specific miRNAs have been found to have critical roles in regulating key pathogenic mechanisms in models of preclinical allergic inflammation (eg, miR-21). Therefore, they might have perspectives as disease biomarkers and therapeutic targets when new miRNA mimics/antagomiRs, and novel small-mol-

TABLE 1

Toll-like receptors (TLR) and TLR agonists under clinical development in allergic diseases

TLR	Exogenous and Endogenous Ligands	TLR Agonists
TLR1	Bacterial lipopeptides	
TLR2	Bacterial lipoproteins and glycolipids	
TLR2/TLR1	Bacterial diacyl lipopeptides	
TLR2/TLR6	Bacterial triacyl lipopeptides	
TLR3	Viral double-stranded RNA	Vaccine adjuvant (Poly I:C)
TLR4	Bacterial LPS	Allergy
TLR5	Bacterial flagellin	
TLR6	Bacterial triacyl lipopeptides	
TLR7	Viral single-stranded RNA	Asthma, allergic rhinitis
TLR8	Viral single-stranded RNA	Allergic rhinitis
TLR9	Bacterial and viral CpG-DNA	Asthma, AR; vaccine adjuvant
TLR10	Unknown	
TLR11	Profilin	

ecule miRNA inhibitors become available for human use.

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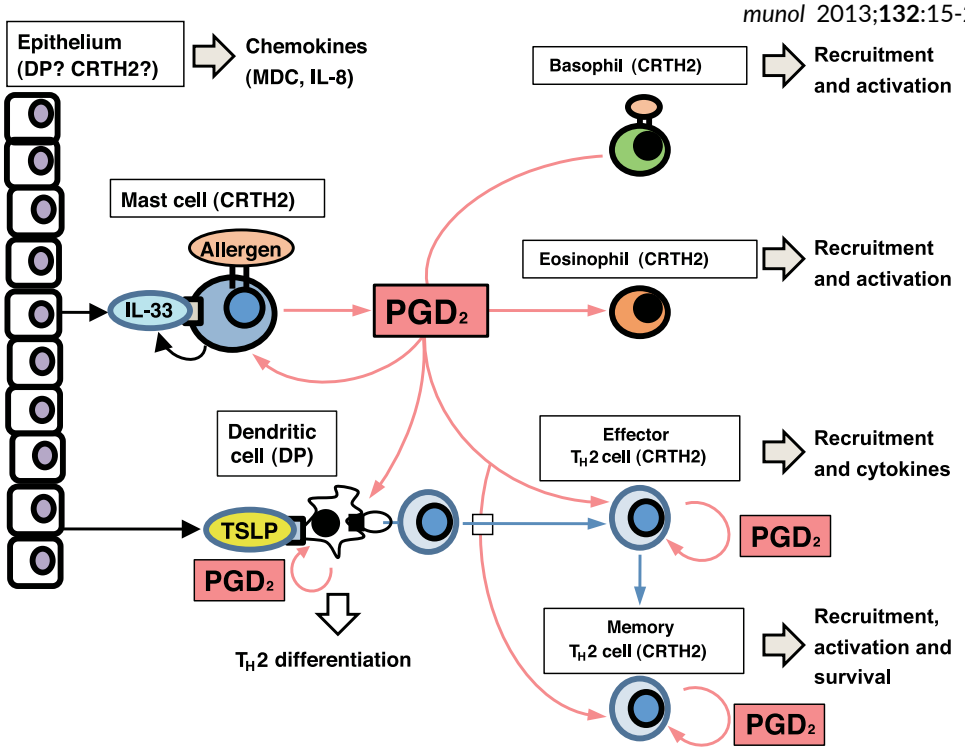

Figure 1 Prostaglandin D2 (PGD2), an arachidonic acid metabolite, is a key mediator in inflammation after allergen exposure and is released by IgE-activated mast cells and other inflammatory cell types. PGD2 helps in recruiting and activating Th2 lymphocytes, eosinophils and basophils. (*From Arima M, Fukuda T. Prostaglandin D_2 and Th2 inflammation in the pathogenesis of bronchial asthma. Korean J Intern Med. 2011; 26:8-18.*)

11 PHARMACOGENETICS OF ALLERGIC RHINITIS

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KEY MESSAGES

- Genetic susceptibility for allergic rhinitis (AR) is not well defined and understudied
- Pharmacogenetic studies in AR are largely missing
- Pharmacogenetic studies investigating response to allergen immunotherapy are needed
- Strategies to identify patients with severe AR to profit from biologicals is needed

Within the "big three" allergic diseases (asthma, atopic dermatitis and allergic rhinitis), allergic rhinitis (AR) is the disease the least targeted and defined by genetic studies. While genome wide analyses are history in asthma and atopic dermatitis (Figure 1) and the field moves on to whole exome and whole genome sequencing, genome wide association studies are still sparse in AR. When it comes to pharmacogenetic studies of AR, current knowledge is almost non-existing. Potential reasons may be that (a) all patients are perfectly treated or even cured by current medication and treatment or that (b) there are no side effects with current therapy so that pharmacogenetic studies to optimize treatment are not needed. Neither (a) nor (b) seems likely the case.

Current standard therapy for AR in most cases and countries is systemic and/or local antihistamines, topic steroids or AIT.

For histamine receptors and genes within histamine related pathway genes, knowledge on common and rare mutations exists, but studies investigating their effects in patients with AR under these therapies is lacking. For steroids, pharmacogenetic studies have been performed, but not considering topic nasally applied steroids in patients with AR. Pharmacogenetic (and pharmacoepigenetic) studies in AIT have never been performed so far, but could be of greatest interest to the whole allergy field as these may lead to the identification of mechanisms related to tolerance induction and individual susceptibility to allergy or tolerance development.

There is a new wave of treatment options on the horizon that may eventually also change clinical practice in AR. With biologicals reaching severe asthma therapy, also patients with AR (at least with an asthma/AR overlap syndrome) will be treated with these targeted approaches. Thus, profiling these patients for mutations in IL13, IL5 and other specific targets of biologicals will be necessary in the future. Obviously, there is a big unmet need for pharmacogenetics in AR to tailor and individualize therapy.

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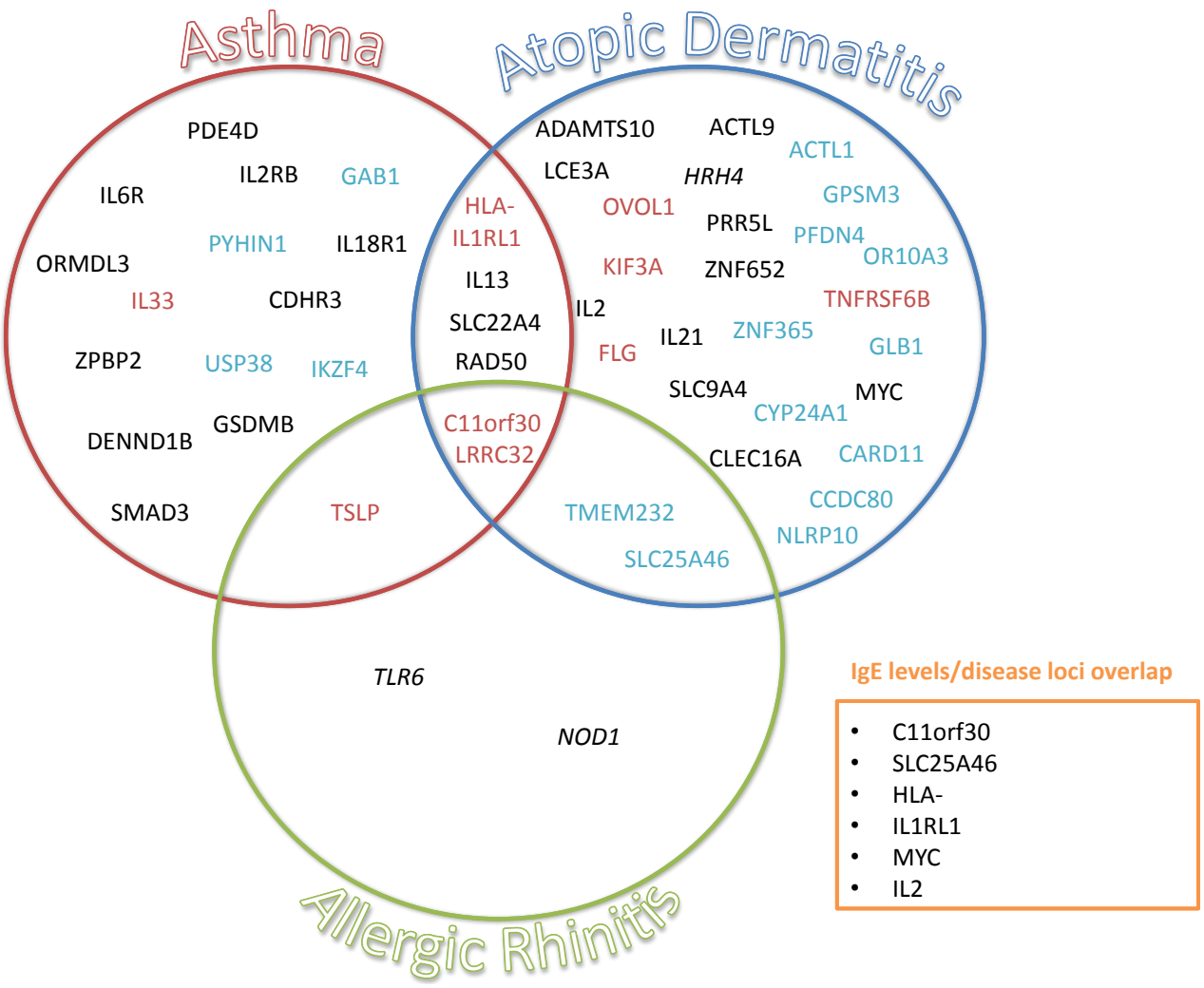

Figure 1 Venn diagram illustrating genes identified through genome-wide association studies as associated with the allergic diseases asthma, atopic dermatitis and allergic rhinitis. Genes highlighted in black identify those discovered in Caucasian populations, with italics defining promising genes that nearly achieved genome-wide significance. Genes highlighted in blue identify those genes discovered in non-Caucasian populations, while those in red identify those genes discovered in both Caucasian and populations of other ancestry. (*Reproduced with permission from Portelli MA1, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome-wide association. Clin Exp Allergy, 2015;45:21-31, with permission from Willey Blackwell.*)

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12 COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR ALLERGIC RHINITIS

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Allergic rhinitis (AR) is one of the most common health problems worldwide. Pharmacologic treatment and allergen immunotherapy (AIT) are the two primary choices in the conventional approach to AR. Outside of these options lies complementary and alternative medicine (CAM). Worries about concurrent side effects of conventional anti-allergic medication could be one of the major reasons for more AR patients to seek help from CAM (Figure 1).

Acupuncture and herbal therapies are current the most popular CAM strategies for AR, followed by vitamin therapy, tea therapy, massage and Ayurveda etc (Table 1). Some of these methods have shown great efficacy in treating AR and others have not. CAMs are supposed to be therapeutic effective via modulating the immune system, by affecting the balance between the Th1 and Th2 cell-derived cytokines.

Acupuncture (Figure 2) and acupressure work via stimulating specific points on the human body. Based on the latest meta-analysis of the studies published from 1980 to 2013, acupuncture appears to be a safe, valid and cost-effective option for allergy

KEY MESSAGES

- Worries about concurrent side effects of conventional anti-allergic medication drive more patients to seek complementary and alternative medicine (CAM) for help
- Acupuncture and herbal therapies are current the most popular CAM strategies for allergic rhinitis (AR). They are supposed to be therapeutic effective via affecting the balance between the Th1 and Th2 response
- Acupuncture can be recommended as adjunct therapy for AR. Other therapies have shown some clinical promise
- In spite of an increasing use of CAMs for AR, both the patients and the medical providers should be fully aware of the limitations of CAMs and to avoid relying too much on CAMs

TABLE 1

Major complementary and alternative approaches for allergic rhinitis

Categories	Examples
Accupuncture	sphenopalatine ganglion stimulation
	acupoint moxibustion
	acupoint catgut implantation
	ear accupuncture
Herbal medicine	herbal formula
	acupoint herbal patching
Vitamin complements	Vitamin D
Others	tea therapy
	massage

** only major approaches are stated here*
** based on database on www.gopubmed.org*

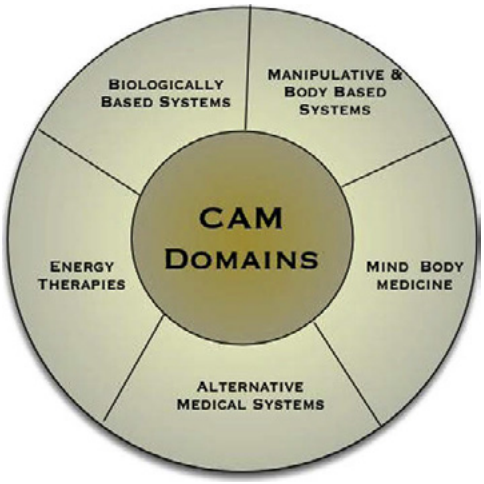

Figure 1 CAM classifications. CAM comprises 5 domains: alternative medical systems, biologically based therapies, manipulative therapies, mind-body therapies, and energy therapies. The alternative medical system involves whole medical systems that are built on other theories and practices including acupuncture, Ayurveda, homeopathic treatment, and naturopathy. Manipulative therapies include chiropractic care and massage. Mind-body therapies use a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms and include biofeedback, meditation, guided imagery, progressive relaxation, deep breathing, hypnosis, yoga, Tai Chi, Qi-gong, Reiki, and prayer. The biologically based therapies use substances found in nature, such as herbs, foods, and vitamins and include megavitamin therapy, various diet-based therapies, folk medicine, chelation therapy, and herbal medicines.3 Energy therapies are essentially made up of biofield therapies that are intended to affect energy fields that purportedly surround and penetrate the human body, whereas bioelectromagnetic based therapies involve the unconventional use of electromagnetic fields. (*Reprinted from J Allergy Clin Immunol, 123/2, Mainardi T, Kapoor S, Bielory L. Complementary and alternative medicine: herbs, phytochemicals and vitamins and their immunologic effects, 283-294, Copyright 2009, with permission from Elsevier.*)

relief, and can be recommended as adjunct therapy for AR. Acupuncture decreases nasal symptom scores and improves quality of life with no serious systemic reaction or side effects. Its efficiency and safety heavily depends on the clinical experiences and skills of the acupuncturists.

Some herbal therapies and antioxidants demonstrate a trend toward some clinical efficacy. A few therapies, including spiruline, butterbur, phototherapy and acupoint herbal patching hold some promise. Herbal medicine, though is widely used for treating AR in China and Asia, is not yet qualified and recommended by the international peers since large studies with appropriate randomization, blinding and control are lacking.

Tea therapy is becoming an easy to take self-care method for AR patients in Asia. Japanese green tea with methylated catechin as an active ingredient has been suggested beneficial for AR patients sensitised to cedar by relieving symptoms, improving quality of life, and by reducing peripheral eosinophil as well.

In conclusion, the popularity of CAM among the general public is increasing, but CAMs have not been integrated into the guidelined for AR treatment yet. Rigorous studies of CAM for AR are very few. Both the AR patients and the medical providers should be fully aware of the limitation of CAMs in order to avoid relying too much on CAM.

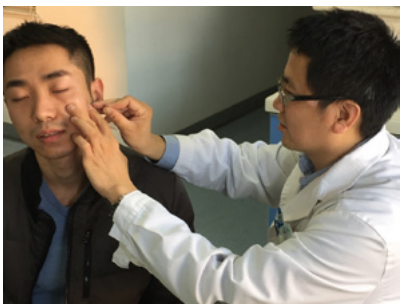

Figure 2 Acupuncturist in practice at AR clinic Beijing Tongren Hospital, China.

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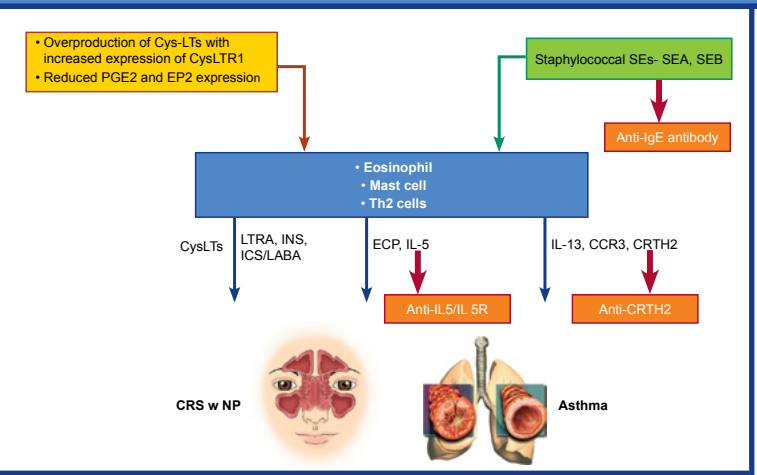
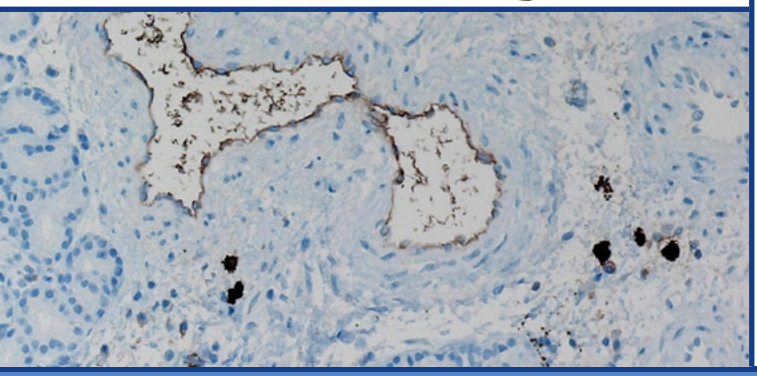
Section F





ALLERGIC RHINITIS - SPECIAL CONSIDERATIONS

* Aspirin-exacerbated respiratory disease
* Nonallergic rhinitis
* Local allergic rhinitis
* Conditions mimicking allergic rhinitis
* Primary ciliary dyskinesia
* Oral allergy syndrome
* Non-allergic, mastocytosis-associated rhinitis (NAMAR)
* Occupational irritant and allergic rhinitis
* Allergic rhinitis in the elderly
* Management of allergic rhinitis during pregnancy
* Allergic rhinitis in children
* Allergic rhinitis in elite athletes
* Rhinitis in a tropical environment
* Severity and control in allergic rhinitis
* Phenotypes and endotypes of allergic rhinitis
* The burden of allergic rhinitis on patients' quality of life
* Adherence to the management plan of allergic rhinitis
* Illness perception, mood and coping in patients with rhinitis
* Pharmacoeconomics of allergic rhinitis

1 ASPIRIN-EXACERBATED RESPIRATORY DISEASE

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Aspirin-exacerbated respiratory diseases (AERD) is a distinct syndrome characterized by moderate to severe asthma, chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), and hypersensitivity to aspirin/non-steroidal anti-inflammatory drugs (NSAIDs). It affects 10-20% of asthmatic patients and about 8-26% of patients diagnosed with CRSwNP. AERD is common in middle-aged women and usually presents with severe CRS and asthma symptoms.

KEY MESSAGES

- Aspirin-exacerbated respiratory diseases (AERD) are characterized by intense eosinophilic inflammation of upper and lower airways, which leads to more severe airway inflammation and a need for more aggressive medical and surgical interventions
- Dysregulation of arachidonic acid metabolism, overproduction of cysteinyl leukotrienes with reduction of PGE_2 is a major pathogenic mechanism of AERD, in which genetic mechanisms regulating with leukotriene synthesis and eosinophil-related genetic polymorphisms are involved
- Local and systemic IgE responses to *Staphylococcal* superantigens contribute to eosinophil activation in the upper and lower airway inflammation
- Inhaled and intranasal steroid, and leukotriene receptor antagonists are recommended as controller medications. Sinus surgery is considered as a next treatment option if medical treatment fails
- Aspirin desensitization can be recommended, if the upper and lower airway symptoms are refractory to medical and surgical treatments. Biologics such as anti-IgE and anti-IL-5 antibodies are suggested as future therapeutic options

PATHOGENIC MECHANISMS

The key features of AERD are the intense eosinophilic infiltration of the upper and lower airway mucosa and the refractory nature to routine pharmacological treatment. Major pathogenic mechanisms are represented by the association between a susceptible genetic background with overproduction of cysteinyl leukotrienes and increased local and systemic IgE (Figure 1). Overproduction of cysteinyl leukotrienes (CysLTs) occurs via activation of 5-lipoxygenase (LO) pathway with decreased level of PGE2. Increased number of platelet-adherent leukocytes was noted, which results in increased production of CysLTs. Local and systemic IgE responses to *Staphylococcal* superantigens contribute to eosinophil activation via polyclonal T and B cell activation with induction of Th2 cytokines and polyclonal IgE production. Genetic studies indicated that HLA DPB1*0301 is a strong genetic marker for AERD. The genetic polymorphisms of leukotriene related genes (CysLTR1, 5-LO,15-LO) and of eosinophil related genes (CCR3, CRTH2, IL-5, IL5R, P2RY12) were reported to be associated with AERD.

DIAGNOSIS

A history of an asthmatic attack after ingestion of aspirin/NSAIDs, or the association of CRSwNP with asthma is suggestive of AERD. A definite *in vitro* diagnostic test is not available, thus

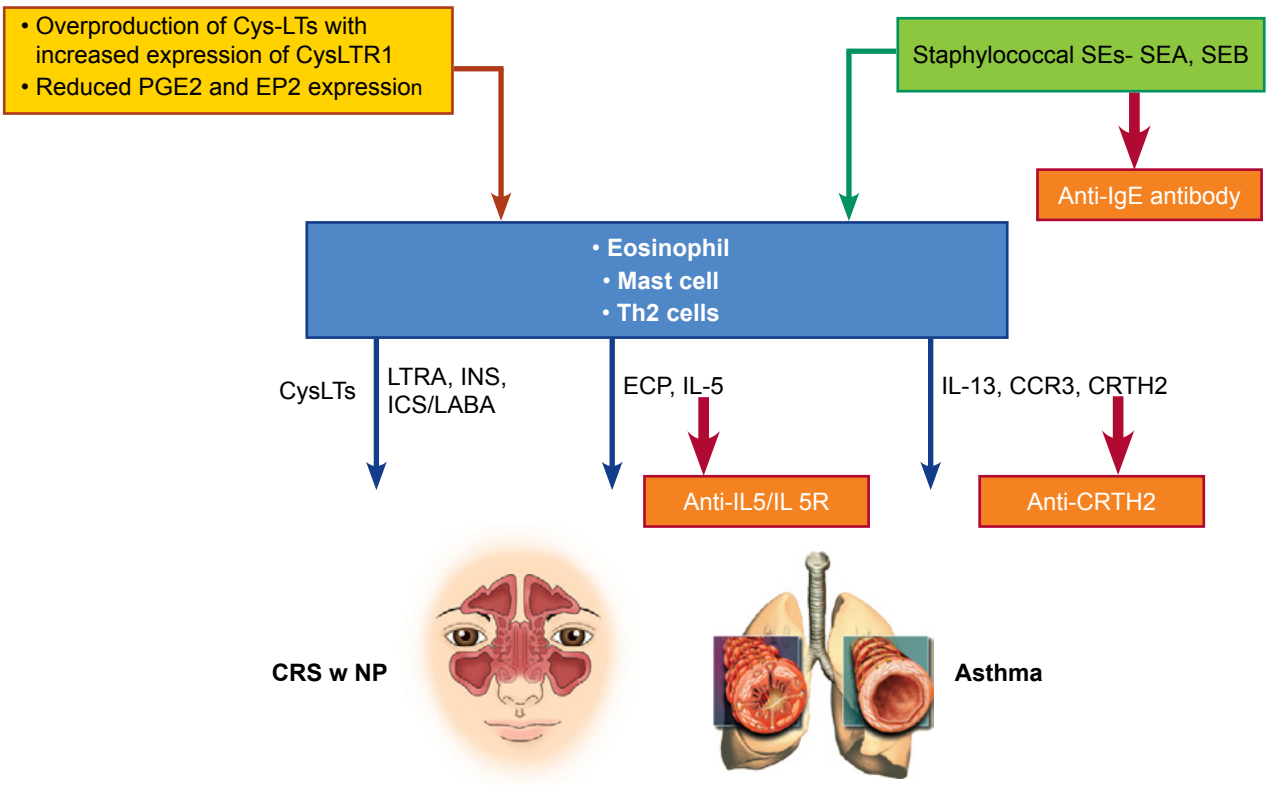

Figure 1 The pathogenic mechanisms and future therapeutic intervention for aspirin exacerbated respiratory disease.

the gold diagnostic test is aspirin challenge tests via variable routes, including bronchial provocation which proved safe and is widely used. Serum periostin and the serin protease dipeptidyl peptidase 10 (DPP10) were suggested as potential serum biomarkers for predicting the phenotype of AERD.

MANAGEMENT

Patients with AERD should be recommended to avoid ingestion of aspirin/NSAIDs. Highly selective COX-2 inhibitors are safer alternatives, although their absolute safety has not been proven yet. Pharmacological treatment is needed to control the severe eosinophilic inflammation of the upper and lower airways. Intranasal steroids, inhaled corticosteroid with/without long acting beta2 agonist and leukotriene receptor antagonists are recommended as controller medications. Sinus surgery is considered as a next treatment option after the medical treatment fails. Aspirin desensitization can be recommended for the CRSwNP patients with AERD who are refractory to medical and surgical treatments.

In conclusion, further efforts are needed to investigate diagnostic biomarkers for early diagnosis of AERD and to evaluate the efficacy of new biologics such as anti-IL-5, anti-IL5R or anti-IgE antibodies.

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2 NONALLERGIC RHINITIS

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KEY MESSAGES

- Non-allergic rhinitis (NAR) is a diagnosis of exclusion comprising several syndromes
- Approximately 50% of patients with chronic rhinitis are non-allergic
- The pathophysiology of the most common form of NAR is unknown (idiopathic rhinitis)
- Management of NAR is not optimal; most commonly used medications include intranasal corticosteroids, azelastine and ipratropium

Non-allergic rhinitis (NAR) is defined as chronic or episodic nasal symptoms in the absence of any evidence of an allergic etiology. It is a diagnosis of exclusion and not a distinct nosologic entity. A number of syndromes have been defined on the basis of clinical characteristics (Table 1), but the pathophysiologic mechanisms behind most of these syndromes have not been elucidated. Infectious rhinitis, including the common cold, and chronic rhinosinusitis are generally not considered under the umbrella of NAR.

When all syndromes are considered, close to 50% of patients, who complain of chronic or episodic nasal symptoms fall under the NAR category. The relative prevalence of NAR, compared to allergic rhinitis (AR), increases with age. Idiopathic rhinitis is the most common NAR syndrome.

Patients with NAR can present with the full constellation of rhinitis symptoms, including rhinorrhea, nasal congestion, posterior nasal drainage, local pruritus and sneezing, but the latter two are less prominent, compared to AR. Also, conjunctival symptoms and asthma co-morbidity are less common in NAR. Another difference between AR and NAR is that patients with the latter condition have lower prevalence of family history of rhinitis or asthma. However, none of these differences can be used as a reliable diagnostic characteristic for NAR. The only diagnostic approach to NAR is the exclusion of allergy either through skin testing or allergen-specific serum IgE measurements. Even when skin testing is negative and allergen-specific serum IgE is undetectable or very low, the possibility exists that local production of IgE at the nasal mucosa may be responsible for a patient's condition. In this instance, and as long as a nasal allergen challenge confirms it, the diagnosis of local allergic rhinitis (LAR) can be given. Ongoing debate as to the prevalence of LAR and the fact that LAR responds well to conventional AR treatment makes it difficult to recommend routine nasal allergen challenge for the differential diagnosis of NAR.

Management of NAR is summarized in Table 1. For syndromes in which the etiology is known (e.g. drug-induced rhinitis), removal of the offending agent is the most logical and effective intervention. In the case of idiopathic rhinitis, treatment should aim towards controlling symptoms since curing the condition is not an option at this point. Azelastine, an intranasal antihistamine, or intranasal corticosteroids should be tried first; intranasal capsaicin may be used in some specialized centers. For patients with excessive rhinorrhea, intranasal ipratropium can offer adequate relief.

TABLE 1

Nonallergic Rhinitis Syndromes: Characteristics, Mechanisms and Management

Nonallergic Rhinitis Syndromes	Subphenotypes	Clinical Characteristics	Mechanisms/Endotypes	Management
Idiopathic Rhinitis Alternative Terms: • Nonallergic, noninfectious perennial rhinitis (NANIPER) • Intrinsic rhinitis • Vasomotor rhinitis • Nonallergic rhinopathy	None identified	• Most prevalent form of NAR • Most common symptoms: nasal congestion, rhinorrhea • Triggers: irritants and/or weather changes (but also chronic symptoms without identifiable triggers)	• Uncertain role of inflammation • Sensorineural hyperreactivity (neurogenic rhinitis)?	• Irritant avoidance • Oral antihistamines ineffective • Nasal antihistamines (azelastine): effective • Intranasal corticosteroids: conflicting results • Capsaicin: effective (small studies)
Nonallergic Rhinitis with Eosinophilia Syndrome (NARES)	None identified	• Most common symptoms: nasal congestion, rhinorrhea, sneezing, pruritus • Nasal secretion eosinophilia	• Related to local allergic rhinitis? • A prodrome to chronic rhinosinusitis?	• Intranasal corticosteroids: effective
Hormonal Rhinitis	• Rhinitis of pregnancy • Menstrual cycle-associated rhinitis	• Most common symptom: nasal congestion • Rhinitis of pregnancy: most common during late pregnancy; smoking is a risk factor	• Estrogen effects on nasal vasculature?	• Rhinitis of pregnancy: Minimal possible intervention for symptom relief
Rhinitis of the Elderly	None identified	• Most common symptom: watery rhinorrhea • Triggers: spontaneous	• Cholinergic nasal hyperreactivity?	• Anticholinergics
Gustatory Rhinitis	None identified	• Most common symptom: watery rhinorrhea • Triggers: hot and spicy foods	• Cholinergic nasal hyperreactivity? • Post-traumatic • Post-surgical • Cranial nerve neuropathy-associated • Idiopathic (most common)	• Avoidance of spicy food • Anticholinergics prior to spicy food
Atrophic Rhinitis	• Primary (warm climates) • Secondary	• Mucosal and glandular atrophy • Bacterial colonization • Perceived nasal congestion • Crusting • Foetor • Hyposmia	• Primary: unclear • Secondary: extensive surgery, chronic granulomatous disorders	• Nasal irrigation • Antibiotics as needed
Cold air-Induced Rhinitis (Skiers' Nose)	None identified	• Most common symptoms: rhinorrhea, nasal congestion, burning • Trigger: cold, windy conditions	• Nasal nociceptor activation by hyperosmolarity and, possibly, low temperature	• Anticholinergics prior to cold air exposure

TABLE 1

Nonallergic Rhinitis Syndromes: Characteristics, Mechanisms and Management (continued)

Nonallergic Rhinitis Syndromes	Subphenotypes	Clinical Characteristics	Mechanisms/Endotypes	Management
Drug-Induced Rhinitis	• Rhinitis medicamentosa • Aspirin-Exacerbated Respiratory Disease (AERD) • Rhinitis induced by systemic alpha and beta-adrenergic antagonists • Rhinitis induced by phosphodiesterase (PDE) V inhibitors • Rhinitis induced by other drugs (ACE inhibitors, calcium channel blockers, antipsychotics)	• AERD includes nasal polyposis and asthma; diagnostic aspirin challenge • Most common symptom of other phenotypes: nasal congestion	• Rhinitis medicamentosa: excessive use of intranasal decongestants (alpha adrenergic agonists) downregulating alpha-adrenergic receptor function • AERD: overproduction of leukotrienes and dysregulation of enzymes and receptors responsible for the production and function of protective lipid mediators • Systemic alpha and beta-adrenergic antagonists: downregulation of nasal sympathetic tone • PDE V inhibitors: increased local concentrations of nitric oxide causing vascular dilatation and congestion • Other drug-induced rhinitis: mechanisms unclear	• Removal of offending drug (if clinically possible) • Rhinitis medicamentosa may be avoidable if nasal corticosteroids are used concomitantly; nasal corticosteroids can be used to facilitate withdrawal of decongestants • AERD: aspirin desensitization followed by long-term aspirin treatment
Occupational Nonallergic Rhinitis	• Irritant-induced rhinitis • Corrosive rhinitis	• Irritant-induced: symptoms subside after a few days away from work	• Irritant-induced: can be associated with neutrophilic inflammation, possibly caused by neuropeptides released locally from sensory nerves • Corrosive: diffuse mucosal damage induced by toxic chemical gases	• Avoidance of causative exposures

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3 LOCAL ALLERGIC RHINITIS

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KEY MESSAGES

- Local allergic rhinitis (LAR) is a new phenotype of allergic rhinitis (AR) characterized by a localized nasal allergic response in patients with negative skin prick-test (SPT) and non-detectable serum specific IgE (sIgE) antibodies
- LAR is an under/misdiagnosed disease that may affect patients from different countries, ethnic groups and ages
- The diagnosis of LAR is based on a clinical history, a positive response to nasal allergen provocation test and/or the detection of nasal sIgE
- SPT and serum sIgE are not sufficient to differentiate between LAR and non-AR
- Subcutaneous allergen immunotherapy has demonstrated to be an effective treatment in LAR

Local allergic rhinitis (LAR) is a clinical entity characterized by nasal itching, sneezing, rhinorrea and obstruction caused by a nasal allergic response to aeroallergens in the absence of systemic atopy (negative skin prick test (SPT) and undetectable sIgE in serum) (Figure 1). LAR is a newly described phenotype of allergic rhinitis (AR) that may starts early in life and persists throughout the years, with a tendency towards clinical worsening and the development of asthma. It is a common respiratory disease, affecting patients from different countries, ethnic groups and ages, with impairment of the quality of life and frequent association to conjunctivitis and asthma. Every physician can see patients with LAR every day during practice and should be prepared to differentiate these patients from non-AR.

Immunologically the nasal mucosa inflammation of LAR patients presents a Th2 cytokine profile with local production of sIgE and increased levels of eosinophils, mast-cells and T cells. Typically there is a positive response to nasal allergen provocation test (NAPT) and NAPT induces the immediate and late phases of the allergic inflammatory response with nasal production of tryptase, eosinophil cationic protein, and sIgE antibodies (Figure 2).

The diagnosis of LAR is based on a clinical history of allergen induced rhinitis symptoms in patients with negative SPT and undetectable serum sIgE followed by the demonstration of an allergic response to aeroallergens by NAPT and/or the detection of nasal sIgE (Figure 3). A detailed clinical history is crucial for identifying patients with LAR. The majority of patients are non-smoking young women, who have moderate to severe rhinitis associated with conjunctivitis and asthma. The onset of the disease in childhood and a family history of atopy are also common in LAR (Table 1). The NAPT is the gold standard for the diagnosis of LAR. It is safe, sensitive, specific, and reproducible, although time-consuming. Fortunately, a new protocol for NAPT with multiple aeroallergens in one session has shortened the diagnosis. The determination of nasal sIgE and the basophil activation test (BAT) are very specific *in vitro* techniques useful for confirming LAR.

LAR patients have a good re-

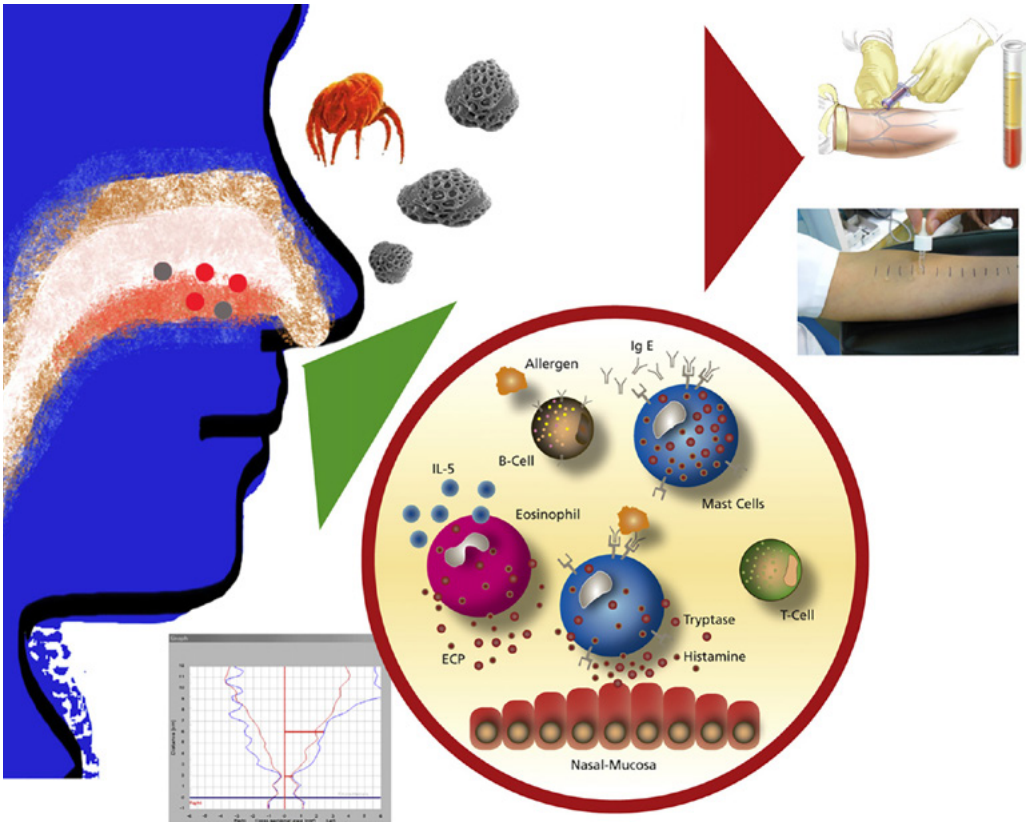

Figure 1 Local allergic rhinitis (LAR) is characterized by a nasal Th2 inflammatory response with local production of sIgE antibodies and positive response to NAPT (green arrow) in patients with a negative skin prick test and absence of IgE antibody in peripheral blood (red arrows). (*Reprinted from J Allergy Clin Immunol, 129/6, Rondón C, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, Mullol J, Blanca M. Local allergic rhinitis: concept, pathophysiology, and management, 1460-1467, Copyright 2012, with permission from Elsevier.*)

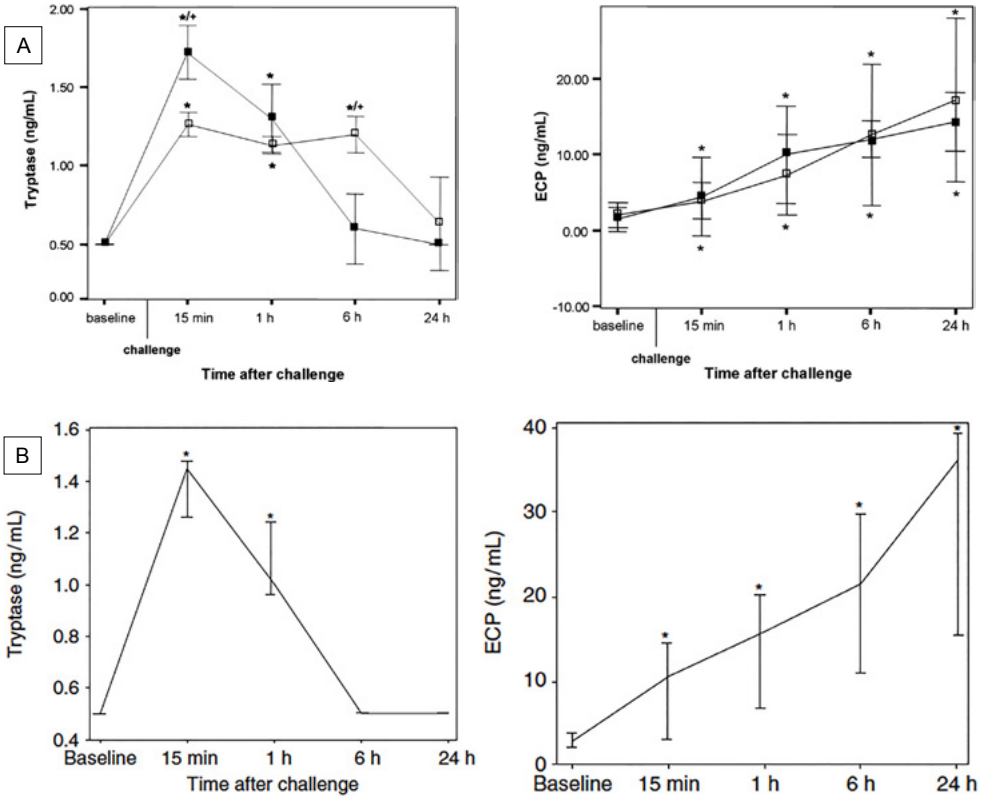

Figure 2 Kinetic of nasal production of inflammatory mediators (tryptase and eosinophil cationic protein (ECP)) after nasal allergen provocation test with grass pollen (figure 2A) and D. pteronyssinus (figure 2 B). (*Figure 2A reprinted from J Allergy Clin Immunol, 124/5, Rondón C, Fernández J, López S, Campo P, Doña I, Torres MJ, Mayorga C, Blanca M. Nasal inflammatory mediators and specific IgE production after nasal challenge with grass pollen in local allergic rhinitis, 1005-1011.e1, Copyright 2009, with permission from Elsevier. Figure 2B reproduced with permission from López S, Rondón C, Torres MJ, et al. Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus in local allergic rhinitis. Clin Exp Allergy 2010;40:1007-1014, with permission from Willey Blackwell.*)

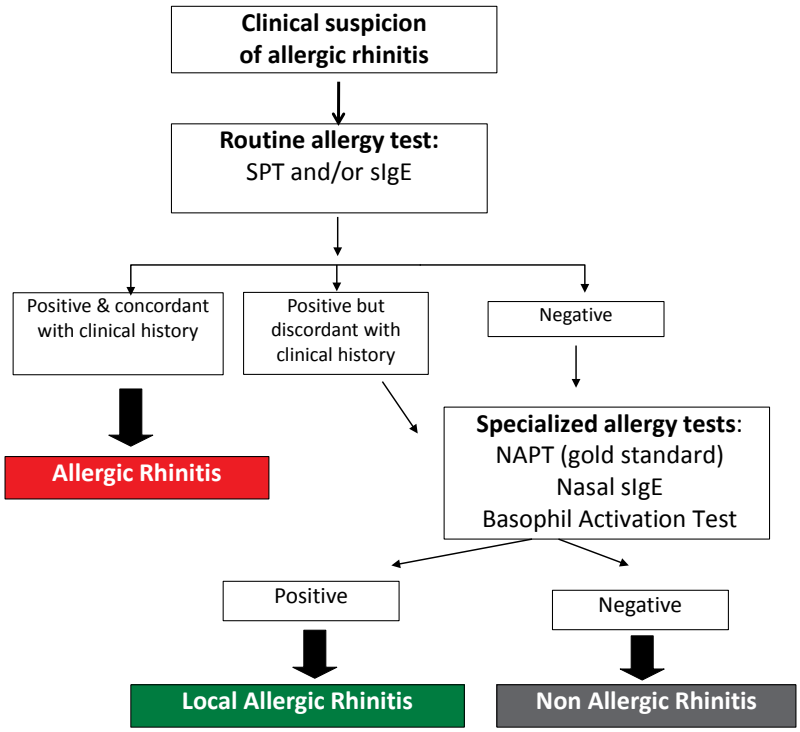

Figure 3 In suggestive cases of AR with negative SPT and serum sIgE, a thorough allergological evaluation (nasal allergen provocation test and/or nasal detection of sIgE and basophil activation test) should be considered to differentiate between LAR and non-allergic rhinitis. (*Adapted from Campo P, Rondón C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in Non-Allergic Rhinitis. Clin Exp Allergy. 2015 May;45(5):872-81.*)

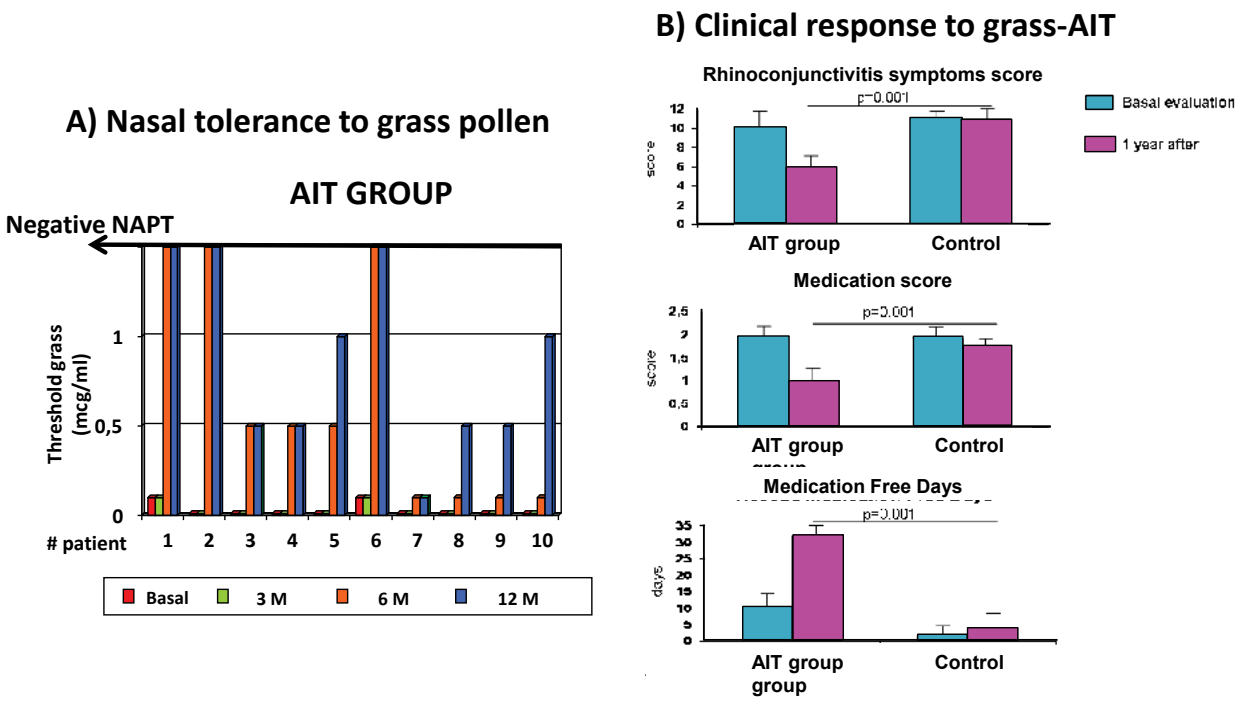

Figure 4 Allergen immunotherapy (AIT) for LAR. The treatment of LAR patients with a course of 6 months of grass specific subcutaneous AIT induced increased tolerance to allergen with negative NAPT in three patients (A), and a clinical improvement in the following spring (B), with reduction in daily rhinoconjunctivitis symptom and rescue medication scores and an increase of the number of medication-free days compared with the control group treated with oral antihistamines and intranasal corticosteroids. (*Adapted from Rondón C, Blanca-López N, Aranda A, et al. Local allergic rhinitis: allergen tolerance and immunologic changes after preseasonal immunotherapy with grass pollen. J Allergy Clin Immunol. 2011 Apr;127(4):1069-71*)

sponse to allergen avoidance measures, and pharmacological treatment with intranasal corticosteroids and oral antihistamines. Ongoing evidence indicate that subcutaneous allergen immunotherapy with grass and house dust mite is beneficial for LAR by reducing the symptoms and the use of rescue medication, and by increasing immune tolerance towards the allergen.

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TABLE 1

Demographic and clinical differences between LAR and non-allergc rhinitis (NAR)

	LAR	NAR	p value
Number of patients	110	48	
Age (y)	**29***	42	0.001
Onset age (y)	**21***	36	0.001
Onset in childhood (%)	**36***	9	0.001
Women (%)	78*	52	0.001
Non-smoking habit (%)	81	83	>0.05
Family history of atopy (%)	**44***	21	0.005
Rhinitis classification (%)			
Persistent symptoms	91	85	>0.05
Perennial symptoms	71	77	>0.05
Severity of symptoms			
Mild	5	8	ND
Moderate	36	57	ND
Severe	**59***	35	0.006
Nasal symptom (%)			
Itching	**86***	71	0.031
Sneezing	80	71	>0.05
Nasal obstruction	60	90*	0.001
Mucous rhinorrea	22	**71***	0.001
Main trigger factors (%)			
House dust	**47***	19	0.001
Irritant	19	**46***	0.001
Comorbidites (%)			
Conjunctivitis	65	50	>0.05
Asthma	31	18	>0.05

Continuous variable are expressed as mean

*LAR: local allergic rhinitis; NAR: non-allergic rhinitis; y: years * p <0.05. (Table adapted from Rondón C, Campo P, Galindo L, Blanca-López N, Cassinello MS, Rodriguez-Bada JL, Torres MJ, Blanca M. Prevalence and clinical relevance of local allergic rhinitis. Allergy. 2012 Oct;67(10):1282-8.)*

4 CONDITIONS MIMICKING ALLERGIC RHINITIS

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KEY MESSAGES

- Several conditions that are mimicking allergic rhinitis (AR), such as chronic rhinosinusitis (CRS), are partly associated with rhinitis symptoms
- The prevalence of rhinitis symptoms or skin prick test positivity are high, which might lead to delay in diagnosing a condition mimicking AR
- Some conditions mimicking AR need fast detection and treatment such as nasal foreign body, tumor and cerebrospinal fluid leakage

Several conditions mimick allergic rhinitis (AR) (Table 1). The inflammation of the nasal mucosa may or may not associate these conditions. Rhinitis is a prevalent disorder, whereas some mimicking conditions are rare. This may cause delayed diagnosis of the mimicking disorders.

Inflammation close to the nasal cavity usually leads to inflammation of the nasal mucosa. Examples include rhinosinusitis, inflammation of the oral cavity, such as dental caries and periodontal disease, rare infections such as tuberculosis, fungal sinusitis, Lyme disease, meningitis and autoimmune diseases such as Wegener´s granulomatosis and Sjogren's syndrome. In children, the most common disorders mimicking rhinitis are adenoid hypertrophy and intranasal foreign body.

Sniffling, a habit rhinitis may develop in children after a cold or other irritant. These rhinitis symptoms disappear during sleep. Dysfunction of autonomous nervous system may lead to rhinitis. Psychosocial stress may affect rhinitis via the neuro-endocrine system. Depression and other psychiatric disorders may generate or modify rhinitis symptoms.

Tumors and congenital defects, such as choanal atresia, primary ciliary dyskinesia or cystic fibrosis are rarely associated with rhinitis symptoms. It is important to avoid delayed diagnosis of benign and malignant tumors. Treatment-resistant or unilateral rhinitis symptoms should raise suspicion of a tumour. Such tumors include inverted papilloma, olfactory neuroblastoma, juvenile angiofibroma, hemangioma, squamous cell carcinoma, lymphoma, tumors irritating trigeminal nerve, and central lesions.

Structural abnormalities, such as nasal septum deviation, hypertrophic inferior turbinate and valvular insufficiency, often exist together with rhinitis. Spontaneous or traumatic defect of the skull base may cause cerebrospinal rhinorrhea.

Head and facial pain, headache and decreased olfaction are important signs in the differential diagnosis between AR and chronic rhinosinusitis. Other important signs to exclude mimickers are muco-purulent discharge, nasal bleeding, systemic symptoms such as low grade fever and malaise, severe and treatment resistant rhinitis symptoms or unilateral symptoms.

In conclusion, several rhinitis-mimicking conditions may exist with or without inflammation of the nasal mucosa. Their early detection will essentially improve health.

TABLE 1

Conditions mimicking rhinitis	
Congenital defects	Primary ciliary dyskinesia Cystic fibrosis Choanal atresia Other
Structural abnormalities	Adenoid hypertrophy Septum deviation Septal perforation Hypertrophic inferior turbinate Valvular insufficiency Other
Inflammation in neighboring organs	Sinusitis Otitis Tonsillitis Dental caries Periodontal disease Pharyngitis Laryngitis Bronchitis Pneumonia Esophagitis Other
Autoimmune and autoinflammatory diseases	Eosinophilic granulomatosis with polyangiitis (allergic granulomatosis or Churg Strauss syndrome) Wegener´s granulomatosis Sarcoidosis Amyloidosis Sjogren's syndrome Chronic fatigue syndrome Thyroiditis Other
Rare infection	Fungal sinusitis Tuberculosis Lyme disease Syphilis Meningitis Encephalitis Other
Tumors	
Benign	Inverted papilloma Hemangioma Osteoma Fibrous dysplasia Angiofibroma Meningioma Other
Malignant	Squamous cell carcinoma Transitional cell carcinoma Adenocarcinoma Adenoid cystic carcinoma Melanoma Olfactory neuroblastoma Undifferentiated carcinoma Soft-tissue sarcoma Rhabdomyosarcoma Leiomyosarcoma Fibrosarcoma Liposarcoma Angiosarcoma Myxosarcoma Hemangiopericytoma Connective tissue sarcoma Chondrosarcoma Osteosarcoma Synovial sarcoma Lymphoma Plasmacytoma Giant cell tumor Metastatic carcinoma Glioma Tumor affecting trigeminal nerve or orbit
Neurological conditions	Migraine Tension headache Cluster headache Neuropathic pain (trigeminal neuralgia) Atypical facial pain Autonomous nerve dysfunction Repeated facial spasm (Tic) Parkinson's disease Multiple sclerosis Syringobulbia Other
Psychosocial disorders	Psychogenic rhinitis (Habit rhinitis) Psychosocial stress Anxiety disorders Depression Bipolar disorder Psychosomatic syndrome Psychosis Other
Other	Trauma Foreign body Cerebrospinal fluid leak Rhinolith Prominent nasal cycle Gastro esophageal reflux disease Temporo-mandibular joint dysfunction Disease or irritation of the orbit Obstructive sleep apnea

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5 PRIMARY CILIARY DYSKINESIA

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KEY MESSAGES

- Primary ciliary dyskinesia (PCD) is a genetically heterogeneous recessive disorder of motile cilia that leads to sino-pulmonary disease, serous otitis media and infertility. Organ laterality defects occur in ~50% of cases
- Respiratory and nasal symptoms typically start in infancy
- There is no single 'gold standard' diagnostic test. Patients require referral to highly specialised centres where a panel of complimentary sophisticated investigations is available
- The evidence base for treating PCD is limited, and approach is largely based on local experience

Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous recessive disorder of biogenesis, structure and/or function of motile cilia. Ciliated epithelial cells line the airways, nasal and sinus cavities and Eustachian tube. In healthy individuals, mucociliary clearance (MCC) occurs as cilia beat in a co-ordinated pattern, propelling mucus to the oropharynx where it can be swallowed (Figure 1). Impaired MCC in patients with PCD is a consequence of abnormal ciliary beat function, which is usually but not always associated with abnormal ciliary axoneme structure as seen with transmission electron microscopy (TEM) (Figure 2). Mutations in over 30 genes, accounting for ≈65% of cases, have been published to date.

Estimates of prevalence vary widely due to the broad range of non-specific clinical symptoms, variation of mutations in different populations and under-diagnosis. It has been estimated that PCD occurs in approximately 1:10,000 Europeans, and is higher in certain consanguineous populations.

SYMPTOMS OF PCD

Clinicians should refer patients with symptoms suggestive of PCD (Table 1) to a specialist diagnostic centre. Early onset of daily respiratory symptoms is a key feature of PCD. Patients typically present as neonates with respiratory distress, which may range from mild transient tachypnoea to respiratory failure requiring prolonged ventilatory support. Neonatal rhinitis is also common. A persistent wet cough and recurrent respiratory infections continue throughout childhood and adulthood, often with exacerbations during infections. Bronchiectasis can present in infancy and is almost invariable by adulthood, predominantly affecting lower and middle lobes.

Most patients have persistent rhinitis, and radiographic evidence of chronic pan-sinusitis is apparent in childhood. Serous otitis media often fluctuates and frequently is associated with transient impaired hearing that rarely evolves into permanent hearing loss. The structure of sperm flagella is similar to the ultrastructure of cilia, accounting for male infertility, which is common in PCD. Dysfunction of nodal cilia, important for left-right asymmetry during embryonic development, accounts for *situs inversus* in ≈50% and *situs ambiguous* in ~10% of patients.

DIAGNOSIS

Diagnosis of PCD is challenging, with no 'gold standard'. The composite of tests contributing to the diagnosis include measurement of nasal nitric oxide, assessment of ciliary function by high-speed vid-

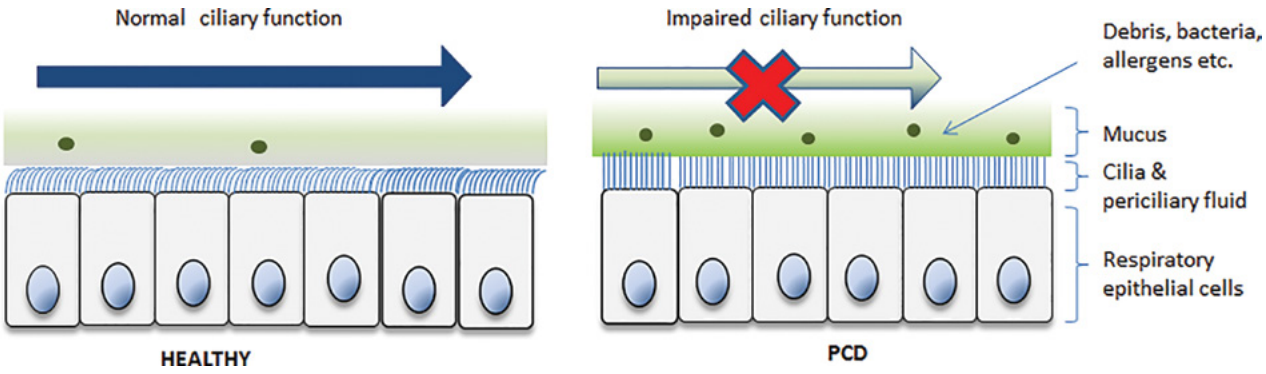

Figure 1 Cilia lining the upper and lower airway of healthy individuals beat in a coordinated sweeping pattern, moving mucus with entrapped particles including pathogens and debris towards the oropharynx for swallowing or expectorating. In PCD cilia do not beat effectively, and mucus and debris fail to be cleared by mucociliary clearance (MCC). (*Image provided by Robert Scott*)

TABLE 1

Who to refer for diagnostic testing
Refer if >2 of these symptoms or, in isolation if other reasons for higher index of suspicion eg. very early onset of symptoms, consanguineous background.
Neonatal respiratory distress of unknown cause
Sibling with PCD, particularly if symptomatic
Situs inversus totalis or other laterality defect, including cardiac disease associated with heterotaxy (situs ambiguous)
Daily wet cough starting in early childhood
Unexplained bronchiectasis
Persistent serous otitis media
Persistent rhinitis and/ or sinusitis
Male infertility

eo microscopy, ciliary ultrastructure by TEM and genetics testing. Performance and interpretation of these tests is not straightforward and should be conducted in centres with extensive experience of normal and abnormal findings.

MANAGEMENT

There is a lack of evidence for the optimal management of PCD with no long-term randomised trials of treatment. As a result, patient care is usually based local experience with other diseases (eg. cystic fibrosis or sinus disease) despite differing underlying pathophysiology. Specialists agree that multi-disciplinary care, with an aggressive approach to airway clearance and management of infections is important for prognosis. However, wide variations in approach to specific treatment exist, for example ventilation tubes are commonly used in some countries to manage serous otitis media.

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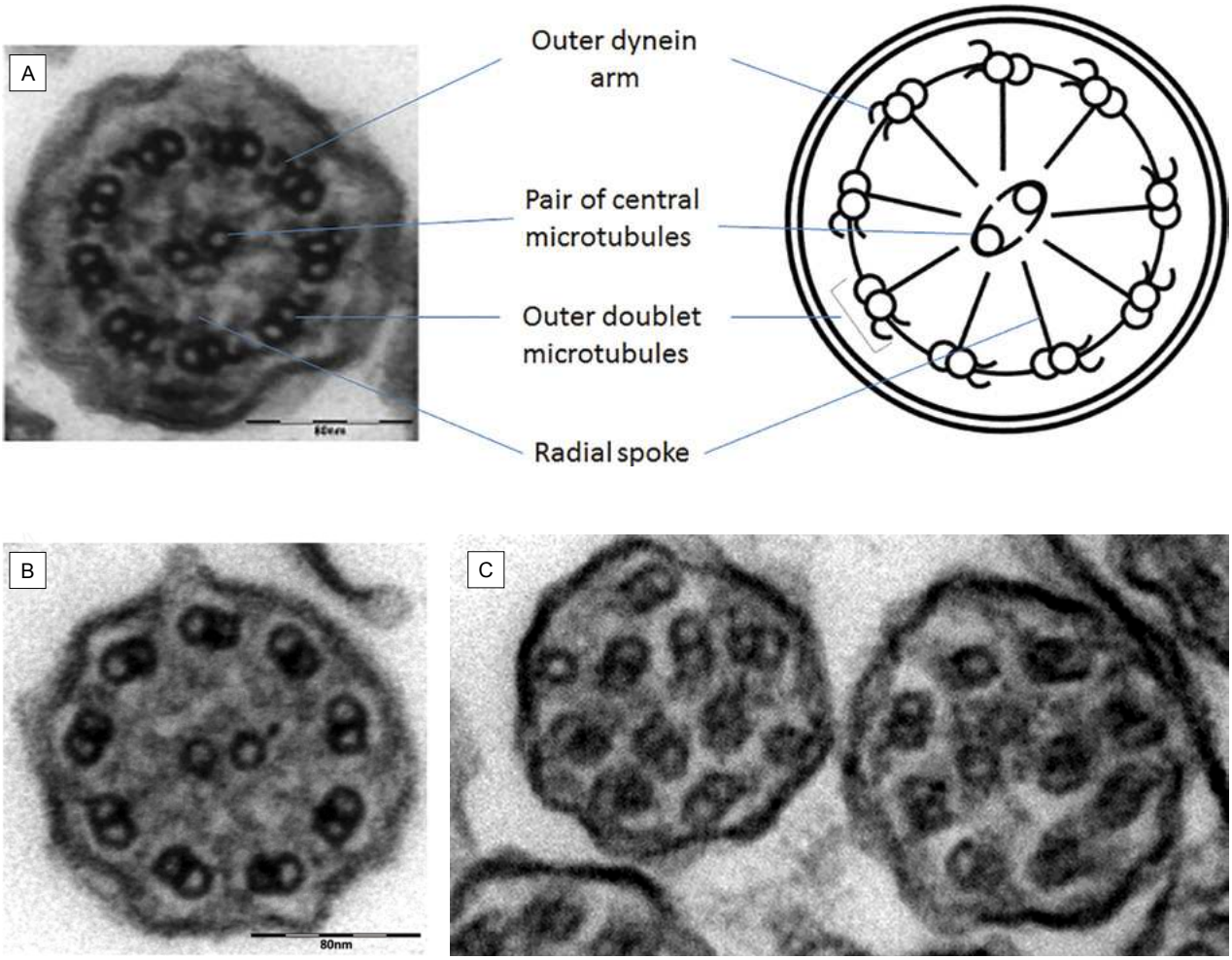

Figure 2 Transverse section of a respiratory cilium as seen by TEM. a) motile cilia in the respiratory tract have a highly organized "9+2" arrangement with nine peripheral microtubule doublets surrounding a central pair of single microtubules running the length of the ciliary axoneme. Nexin and radial spokes support the structure. Attached to the peripheral microtubules are inner and outer dynein arms. Dynein is a mechano-chemical ATPase responsible for generating the force for ciliary beating. Abnormalities of the dynein arms, or of the structures maintaining the 9+2 arrangement impair normal ciliary beating, preventing normal mucociliary clearance. b) TEM of motile cilia from patients with PCD due to an outer dynein arm defect and (c) disorganized ciliary structure. (Schematic image provided by Robert Scott; EM images obtained using FEI Tecnai 12 transmission electron microscope (FEI UK Limited, Cambridge, UK) at80 kV). Scale bars580 nm. EM images provided by P. Goggin (*Primary Ciliary Dyskinesia Group, University Hospitals Southampton NHS Foundation Trust, Southampton, UK*).

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6 ORAL ALLERGY SYNDROME

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The oral allergy syndrome, (OAS) is an IgE-mediated food allergic disorder frequently associated with allergic rhinitis (AR) with sensitisation to pollen allergens. A subgroup of pollen allergic patients, are sensitized to profilin (a pan-allergen present in all vegetables), and are prone to suffer from OAS. These patients are frequently encountered in areas with intense grass pollinization.

In Northern and Central Europe, birch pollen allergic patients may develop OAS with symptoms induced by apple, hazelnut, kiwifruit, pear, carrot, celery and raw potato. In the Mediterranean area, pollen allergic patients may experience OAS with fruits of *Rosaceae* family (peach, apricot, plum, strawberry, cherry, nectarine, pear, apple) (Figure 1). Sometimes, patients allergic to nuts, legumes, animal foods such as cow's milk, egg, fish and shellfish can suffer OAS.

The observed cross-reactivity between pollen and plant foods causing OAS can be correlated with sensitization to a small number of well known allergens (Table 1). Homologues from the major birch pollen allergen, Bet v 1 and profilin, Bet v 2, are present in a

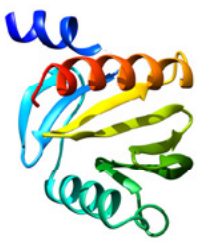
KEY MESSAGES

- Oral allergy syndrome (OAS) is an IgE-mediated food allergic disorder frequently associated with allergic rhinitis with sensitisation to pollen allergens
- Usually symptoms are rather mild and restricted to the oral mucosa
- Most of OAS reactions are mediated by the pan-allergens PR 10 (Bet v 1) and profilin (Bet v 2) and linked with pollen allergies

Figure 1 Fruits of Rosaceae family (peach, apricot, plum, strawberry, cherry, nectarine, pear, apple) inducing oral allergy syndrome in pollen allergic patients in the Mediterranean region. (*Image from Banco de imágenes en Alergología - Spanish Society of Allergology and Clinical Immunology (SEAIC).)*

TABLE 1

Difference between basophils and mast cells			
PR10 associated food allergies		**Profilin associated food allergies**	
Rosaceae			
Apple	Mal d 1	Apple	Mal d 4
Peach	Pru p 1	Peach	Pru p 4
Cherry	Pru av 1	Cherry	Pru av 4
Pear	Pyr c 1	Pear	Pyr c 4
Apiaceae			
Carrot	Dau c 1	Carrot	Dau c 4
Celeriac	Api g 1	Celeriac	Api g 4
Corylaceae			
Hazelnut	Cor a 1.04	Hazelnut	Cor a 2
Others			
Kiwifruit	Act d 8	Kiwifruit	Act d 9
Peanut	Ara h 8	Peanut	Ara h 5
Soybean	Gly m 4	Soybean	Gly m 3
		Melon	Cuc m 2
		Orange	Cit s 2



range of fruits, nuts, tree nuts and vegetables causing the birch pollen-fruit syndrome. For melon and banana allergy profilin sensitization is the predominant sensitizer. In contrast, for the Mediterranean Rosaceae fruit allergy, sensitization to profilin may account for OAS linked symptoms, while for more severe food allergy symptoms the non-specific lipid transfer proteins are the main inducers allergens. Many raw plant foods contain allergens belonging to these three pan-allergen groups. Normally the patient's sensitization profile follows the geographical distribution mentioned above.

The symptoms of OAS include pruritus, tingling, and erythema or angioedema of the lips, tongue, palate and throat. Sometimes, pruritus appears in the ears or tightness in the throat is present. Symptoms appear within 15 minutes after ingestion of foods, normally fresh fruits or vegetables, and are usually mild and disappear spontaneously without any kind of treatment.

Occasionally, OAS may be the first symptom of other food allergy manifestations (cutaneous, digestives, respiratory), even anaphylaxis.

Diagnosis of OAS is based on case history, skin prick testing preferably performed as prick to prick with raw food sources, and determination of specific IgE by *in vitro* tests. Assessment of sensitization patterns to inhalant allergens/pollens can be helpful. Component resolved diagnosis to pan-allergens (Bet v 1, Bet v 2, Pru p 3) could provide valuable additional information. If the patient's history is unclear, a mucosal and/or oral challenge test should be performed, especially for patients at risk to develop severe food allergy symptoms such as anaphylaxis.

An elimination diet of the causative food is recommended based on conclusive diagnosis, discriminating between sensitization patterns with and without clinical symptoms. Dietetic counseling should be offered to the patient how to avoid the incriminating food and if necessary to supplement with vitamins. Usually no symptomatic treatment is required for OAS. Symptoms may improve with pollen allergen immunotherapy, but no solid clinical evidence is available.

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7 NON-ALLERGIC, MASTOCYTOSIS-ASSOCIATED RHINITIS (NAMAR)

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Systemic mastocytosis (SM) is a clonal proliferative disorder of mast cells (MC) that causes pathological accumulation of mast cells in various tissues, which results in a multitude of clinical symptoms due to MC mediator release. Nasal complaints in SM have been described in previous studies as the most frequent allergy-suggesting symptoms. Evidence of allergy could only be found in approximately one half of the patients. Therefore, non-allergic rhinitis symptoms in SM patients have been assumed to be due to an increased nasal mast cell burden. To prove this hypothesis, we investigated whether nasal complaints in non-allergic SM patients are correlated with objective measures of nasal mast cell burden. Eleven adult patients with systemic mastocytosis underwent a comprehensive rhinologic work-up. All patients fulfilled the clinical ARIA criteria for rhinitis. The allergologic work-up included skin prick testing, testing for serum specific IgE, determination of tryptase levels (serum and nasal secretion), and nasal provocation testing. Ten out of eleven SM patients with clinical persistent allergic rhinitis were found to be non-allergic.

KEY MESSAGES

- Non-allergic persistent rhinitis is a frequent finding in systemic mastocytosis
- Nasal itching, sneezing, and rhinorrhoea are the predominant nasal symptoms in this patient group
- The level of nasal tryptase correlates strongly with the main symptoms and could link up the individual local mast cell burden with the individual nasal complaints
- Based on the significance of this mastocytosis-associated symptom complex and elevated nasal tryptase levels, this entity is defined as non-allergic, mastocytosis-associated rhinitis (NAMAR)

The clinical symptom pattern in SM patients with non-allergic persistent rhinitis was quite in contrast with the usually predominant symptoms in persistent allergic rhinitis (AR): nasal obstruction was almost negligible, while itching, sneezing, and rhinorrhea were the predominant symptoms in this patient group. All three predominant symptoms were strongly correlated with the nasal tryptase level, but not with the level of serum tryptase (Figure 1 and Table 1). The level of nasal tryptase correlated strongly with the above mentioned main symptoms and provided the link between the individual local mast cell burden and the individual nasal complaints. The correlations be-

TABLE 1

Mastocytosis-associated nasal complaints	
Nasal symptom	**Correlation (significance) with nasal tryptase level (p values)**
Rhinorrhea	p = 0.017
Sneezing	p = 0.001
Itching	p = 0.003
Obstruction	p = 0.51

Data from Dollner R, Taraldsrud E, Iversen K, et al. Non-allergic, mastocytosis-associated rhinitis. Clin Exp Allergy 2013;43:406-412.

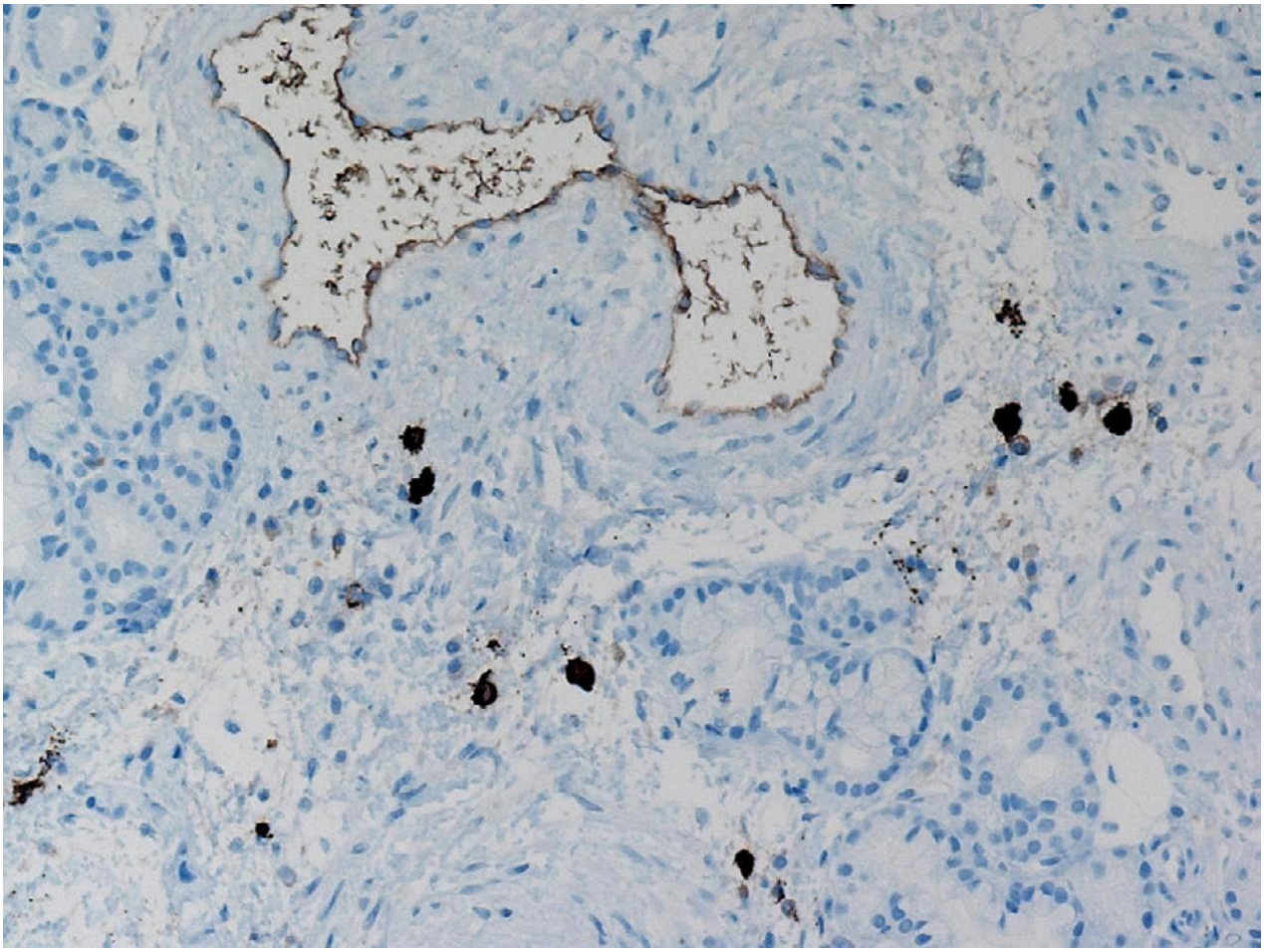

Figure 1 Immunohistochemical staining (tryptase) for mast cells in the nasal mucosa (magnification 40x). (*Picture by courtesy of Dr. Svetlana Tafjord, Oslo University Hospital, Oslo, Norway.*)

tween nasal tryptase and median nasal symptom score respectively rhinorrhea, sneezing, and itching point to mast cell degranulation as the causal factor for rhinitis in MC patients. Thus, elevated nasal tryptase can be recommended as an indicator for mastocytosis-associated non-allergic rhinitis.

The clinically relevant complex of mastocytosis-associated nasal complaints are characterized by:

1) Persistent non-allergic nasal complaints, such as watery rhinorrhea, sneezing, and itching.
2) Elevated nasal tryptase as an objective measure.

Based on the demonstrated significance of this mastocytosis-associated symptom complex, we proposed these criteria to tentatively define the entity of non-allergic mastocytosis-associated rhinitis (NAMAR).

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8 OCCUPATIONAL IRRITANT AND ALLERGIC RHINITIS

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KEY MESSAGES

- Work related rhinitis encompasses both occupational rhinitis (OR) and work-exacerbated rhinitis
- Allergic OR is characterized by nasal and ocular symptoms due to IgE-mediated sensitization to a high molecular weight allergens or low molecular weight chemical sensitizers acting as haptens, through exposure in the work environment
- Risk factors for development of OR include level and length of exposure, atopy, and smoking

Work related rhinitis (WRR) describes a variety of conditions, where nasal symptoms are triggered from exposure to allergens, chemical sensitizers, and/or irritants encountered in the work environment. WRR can be further classified into occupational rhinitis (OR) and work-exacerbated rhinitis (WER) (Figure 1). OR is defined as rhinitis triggered by a specific substance or exposure encountered in the work environment. Reactive upper airways dysfunction syndrome (RUDS), a non-allergic form of OR, is induced by accidental exposure to high levels of irritants or chemical fumes in the workplace. OR should be distinguished from WER, a preexisting rhinitis condition (e.g. allergic rhinitis), that is worsened by exposures in the work environment.

OR may be due to both allergic and non-allergic mechanisms. It is most often associated with allergic sensitization to high molecular weight (HMW) protein allergens. Less commonly, low molecular weight (LMW) chemical sensitizers can form haptens with respiratory proteins and elicit typical allergic rhinoconjunctivitis symptoms at work.

Allergic OR is characterized by nasal and ocular symptoms due to an agent in the workplace, which has induced IgE-mediated sensitization. Development of allergic OR symptoms may be preceded by a latency period of exposure of months to years. Demonstration of allergic sensitization is necessary to confirm allergic OR by a positive skin prick test and/or elevated serum-specific IgE to the suspect workplace allergen(s). A few reactive chemicals, such as the acid anhydrides and platinum salts, have the capacity to haptenize, forming allergenic epitopes and specific IgE responses. After a latency period of exposure to these chemicals, affected workers develop IgE-mediated OR and occupational asthma symptoms.

RUDS, a phenotype of non-allergic OR, is chronic rhinitis related to an acute exposure to a chemical irritant or combustion products. RUDS is not preceded by a latency period. Nasal pathology in RUDS is characterized by focal epithelial desquamation, glandular hypertrophy, lymphocytic infiltrates, and sensory nerve fiber proliferation. Substance P released from sensory nerves, and not histamine, is the hypothesized as the major mediator involved.

Risk factors for development of OR include level and length of exposure, atopy, and smoking. Occupational asthma (OA) and OR are closely associated and coexist 76% to 92% of the time. OR symptoms typically precede those of OA in workers exposed to HMW agents or LMW agents.

A diagnosis of OR can be established by a consistent medical

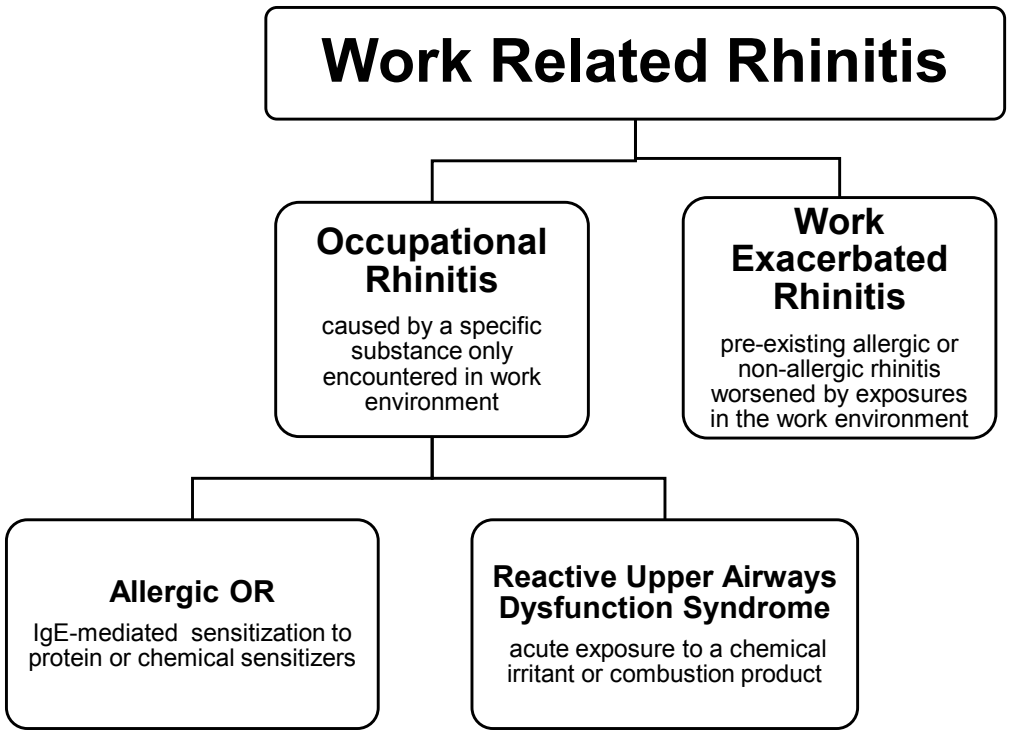

Figure 1 Classification of work related rhinitis.

history of WRR combined with demonstration of allergic sensitization to specific substance(s) encountered in the workplace. Typical rhinitis and eye symptoms exacerbated by the work environment and resolving over weekends and/or during vacations are highly consistent with allergic OR. Patients presenting with rhinitis symptoms at work should be evaluated for non–work-related allergic rhinitis caused by common environmental allergens, which may be confused with OR, but is more consistent with nonspecific WER. An accurate diagnosis of OR and the ability to distinguished it from WER may have important medico-legal consequences.

The principles of management of WRR follow the same principles as for allergic rhinitis: avoidance of exposure, pharmacotherapy and allergen immunotherapy (AIT). Steps to modify the workplace could include: improved ventilation to remove offending exposures, using less hazardous materials, and creating closed-circuit manufacturing processes. Workers should be supplied with high-efficiency personal respirators. Nasal steroids are first line therapy for persistent symptoms. Antihistamines are used for intermittent symptoms or as ancillary agents to nasal steroids. AIT can be considered in patients with OR who fail pharmacotherapy and cannot avoid the causative allergen. Due to the limited availability of commercial allergen extracts for AIT for many forms of allergic OR, indications for AIT are limited.

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9 ALLERGIC RHINITIS IN THE ELDERLY

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KEY MESSAGES

- As the geriatric population continues to increase, healthcare professionals will need to address the growing number of elderly with allergic rhinitis (AR)
- Understanding the pathophysiology of AR in the aging nose is important to properly manage the condition
- In elderly patients with atopic conditions, serum IgE levels stay increased into advanced age
- Two relevant differentials for AR in the elderly are drug-induced rhinitis and common neurologic disorders such as Parkinson's and Alzheimer's
- Treatment involves avoidance of exposure, pharmacotherapy and allergen immunotherapy

The world's geriatric population (65 and older) is estimated to increase from 601 million in 2015 to 1.5 billion by 2050. As this population continues to increase, healthcare professionals will need to address the growing number of elderly with allergic rhinitis (AR).

In 2005, the prevalence of AR in the US for ages 65-75 was 7.8%; over 75 was 5.4%. By 2013, Swiss aged 60+ had an atopic rate of 26% for men and 18% for women; AR rates of 13% and 15% respectively. In Poland (2013), similar percentages were found for atopy (26.7%), seasonal AR (12.6%), and perennial AR (17.1%).

Understanding the pathophysiology of AR in the aging nose is important to properly manage the condition and its deleterious affects on quality of life. With increasing age, the nose undergoes changes in its structural components. These normal aging processes of the nose can manifest as rhinologic dysfunction and result in symptoms of postnasal dripping, nasal drainage, sneezing, and olfactory loss (Table 1). In geriatric individuals without atopic conditions, total and specific IgE productions are reduced. However, this is not the case in elderly patients with atopic conditions, and serum IgE levels stay increased into advanced age. It is important, therefore, to assess elderly patients for AR if their history and physical examination findings are consistent with the disease.

Clinical evaluation of older patients with AR should begin with a complete history. Physical examination is also essential and includes assessment of nasal patency, turbinates, straightness of septum, signs of inflammation, and presence of polyps. In addition to the normal changes produced by aging, rhinitis in the aging nose may also include vasomotor, primary atrophic, and gustatory rhinitis. If the history and physical exam raises a suspicion for AR, *in vivo* (skin prick test) or *in vitro* tests may be utilized. Measures of allergic sensitization, such as those seen in *in vivo* or *in vitro* studies, decline with age; however, there is a robust association between allergic sensitization and allergic disease in the elderly.

Two relevant differentials of increasing importance in the elderly are polypharmacy and drug-induced rhinitis, including anti-hypertensives, anti-cholinergics, beta-blockers, and psychotropics. Common neurologic disorders such as Parkinson's and Alzheimer's can initially present as rhinitis,

TABLE 1

Symptoms and pathophysiology associated with the normal aging nose

Symptoms	Pathophysiology
Nasal obstruction	Loss of nasal tip support secondary to fibrous connective tissue weakening in lateral cartilages
	Decrease in nasal cavity volume secondary to septal cartilage weakening and retraction of nasal columella
Increased airway resistance	Decrease in nasal mucosal softness and elasticity secondary to decrease in mucosal estrogen content
Nasal irritation	Decreased intranasal temperature and humidity of inspired air secondary to decrease in submucosal vessel patency
Olfactory dysfunction	Nasal obstruction and inflammation in the olfactory cleft; central and peripheral nerve disorders
Postnasal drip, coughing, and sneezing	Thickened mucus secondary to mucosal epithelium atrophy
	Decrease mucociliary clearance caused by decreased Decreased frequency of cilia movement and thickened mucus

particularly olfactory dysfunction.

Treatment involves three components: avoidance of exposure to known allergens, pharmacotherapy, and allergen immunotherapy (AIT). Pharmacotherapy includes humidification, antihistamines, intranasal steroids, ipratropium bromide, and leukotriene inhibitors. Although the efficacy of AIT in the elderly has not been widely studied, there are some supportive findings. Surgical treatment is a safe and effective option that may include nasal tip, lateral cartilage, and endoscopic sinus procedures, and is associated with improvements in quality of life.

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10 MANAGEMENT OF ALLERGIC RHINITIS DURING PREGNANCY

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KEY MESSAGES

- Allergic rhinitis (AR) may worsen, improve or remain unchanged during pregnancy
- Allergen avoidance is an important part of the treatment of AR
- Skin testing should be deferred until after delivery
- Antihistamines are less effective for the treatment of AR compared with intranasal glucocorticoids

Allergic rhinitis (AR) is usually pre-existing, although it may develop or be recognized for the first time during pregnancy. Patients with AR often report prominent sneezing, nasal pruritus, and watery rhinorrhea, and some have concomitant ocular itching and irritation. Common triggers for allergic rhinitis include dust mites, animal danders, molds, and pollens (Table 1).

If allergy testing was not performed in the past, we recommend that this evaluation should be deferred until after delivery, since skin testing has the potential to induce systemic allergic reactions in highly sensitive patients. Although skin testing is more sensitive for the diagnosis of sensitivities to inhaled allergens, *in vitro* tests for allergen-specific IgE are widely available and may be used for the diagnosis of AR during pregnancy.

TREATMENT

The mainstays of therapy for AR in pregnant patients are avoidance of triggers, oral antihistamines and intranasal glucocorticoids (Table 2). No important differences in efficacy or safety appear to exist between the various intranasal glucocorticoid preparations. Some clinicians choose budesonide, if starting intranasal glucocorticoids for the first time during pregnancy, since it is classified as a category B drug based on reassuring data available for its use as an inhaled preparation. Pregnant women who require antihistamines for AR should generally be treated with a second generation agent such as loratadine (10 mg once daily) or cetirizine (10 mg daily), since these drugs have reassuring animal and human data, are less sedating, and have fewer anticholinergic side effects compared with first generation agents.

Intranasal cromolyn sodium may be considered a first-line therapy for mild AR in pregnancy because of its excellent safety profile. Decongestants are vasoconstrictors that are available as both oral preparations and nasal sprays. Decongestant nasal sprays can be used very briefly (e.g., three days or less) for temporary relief of severe nasal congestion, and some reassuring human data exist for use of intranasal oxymetazoline during pregnancy. However, as noted above, patients should be warned about dependence with prolonged use of decongestant nasal sprays. Oral decongestants are probably best avoided altogether during the first trimester because of a possible increased risk of a rare birth defect, gastroschisis

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TABLE 1

Environmental Control Measures to reduce Exposure to Allergens

Indoor Allergens	Instructions	Level of Evidence
Animal dander	Remove pet from house; if removal not acceptable, keep pet out of bedroom	Consensus judgment
Dust mites	Encase pillow and mattress with impermeable covers; wash sheets and blankets in hot water weekly	Data from several randomized controlled trials
Cockroaches	Do not leave food or garbage exposed; use poison baits or traps rather than chemical agents, which can aggravate asthma	Few randomized controlled trials

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TABLE 2

Environmental Control Measures to reduce Exposure to Allergens

Drug Class	Drug	FDA Class	Adverse perinatal Outcomes
Oral Antihistamines	Azelastine	C	No human data, animal studies show increase in teratogenicity, skeletal abnormalities and fetal death in high doses
	Cetirizine	B	No increase in congenital malformation
	Chlorpheniramine		No increase in congenital malformation
	Dexchlorpheniramine	B	No increase in congenital malformation
	Fexofenadine	C	This active metabolite of terfenedine has been associated with dose related weight gain animal studies.
	Diphenhydramine		No increase in congenital malformation; withdrawal syndrome a risk
	Hydroxyzine		No increase in congenital malformations; withdrawal syndrome a risk
	Loratadine	B	No increase in congenital malformations, low birth weight, or small for gestational age
Decongestants	Oxymetazoline		No increase in congenital malformations; possible uteroplacental insufficiency with higher doses
	Phenylephrine		Associated with club foot, eye/ear malformations
	Phenylpropanolamine		Increase in total and specific congenital malformations in one study, association with gastroschisis and VSD in case-control studies
	Pseudoephedrine		Association with gastroschisis, hemifacial microsmia and small intestinal atresia in some case-control studies
Intranasal Antihistamines	Azelastine		No controlled studies;
	Olapatadine		No controlled data; animal studies reassuring
Intranasal Corticosteroids	Budesonide	B	Substantial reassuring data for inhaled corticosteroids. Risk of increased malformations with high dose, but may be confounding by severity. Most data for budesonide.
	Fluticasone	C	
	Triamcinolone	C	
	Mometasone	C	

Adapted from Schatz M, Zeiger RS, Falkoff R, et al. Asthma and allergic diseases during pregnancy. In: Adkinson NF, Yunginger-JW, Busse WW, et al, editors. Middleton' s Allergy: Principles and Practice 8th. St. Louis:Mosby, 2014; 951-969.

11 ALLERGIC RHINITIS IN CHILDREN

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KEY MESSAGES

- Allergic rhinitis (AR) is a common problem in childhood and impacts negatively on quality of life
- In children and adolescents, AR may present atypically with symptoms associated with comorbidities such as fatigue and snoring
- Non-sedating antihistamines are the first line therapy for mild to moderate AR; where symptoms are more problematical, nasal corticosteroids are likely to be more effective within or without concurrent antihistamine therapy

Allergic rhinitis (AR) is a common problem in childhood and adolescence. While most experience the typical sneezing, itching, watery rhinorrhoea and nasal blockage (Figure 1), other children and adolescents may present atypically with cough or snoring, due to comorbidities. AR impacts negatively on physical, social and psychological well-being of children and adolescents. As well as direct impact of symptoms, indirect effect of sleep disturbance gives daily fatigue and results in impaired school performance.

The differential diagnosis of rhinitis is wide (Figure 2), commonly it needs to be differentiated from infectious rhinitis, typically caused by a viral infection. Less common is non-allergic, non-infectious rhinitis, usually due to irritants such as cigarette smoke or pollution in this age group. Similar symptoms may occur with other conditions such as adenoidal hypertrophy, septal deviation and nasal polyps. Examination by anterior rhinoscopy and allergy tests may help to substantiate a diagnosis of AR.

A wide range of allergens drive AR. Outdoor allergens, such as tree or grass pollens, are typically associated with seasonal AR while indoor ones, such as house dust mite and animal dander, are usually associated with perennial AR. Especially in new onset AR, skin prick testing and specific IgE may be negative to the likely allergen. Avoidance of relevant allergens, where possible may be helpful for AR.

Oral and intranasal antihistamines and nasal corticosteroids are both appropriate for first-line treatment of AR in children, although the latter are more effective (Figure 3). Once-daily forms of corticosteroids are preferred given their improved safety profile. Potentially useful add-on therapies for AR in children include oral leukotriene receptor antagonists, short bursts of a nasal decongestant, saline douches and nasal anticholinergics. Both sublingual and subcutaneous allergen immunotherapy (AIT) is effective for AR in children and teenagers. There is also some evidence to suggest that AIT may prevent the progression of AR to asthma. Compliance with AR therapy has not been well studied in children and teenagers. It is likely to be suboptimal, particularly for nasal sprays or AIT, and deserves more attention.

The European Academy of Allergy and Clinical Immunology Taskforce position paper on Rhinitis in Children describes the evidence-base for the diagnosis and management of paediatric allergic and non-allergic rhinitis. The position paper also outlines the areas that need to be clarified in the management of rhinitis in children and adolescents.

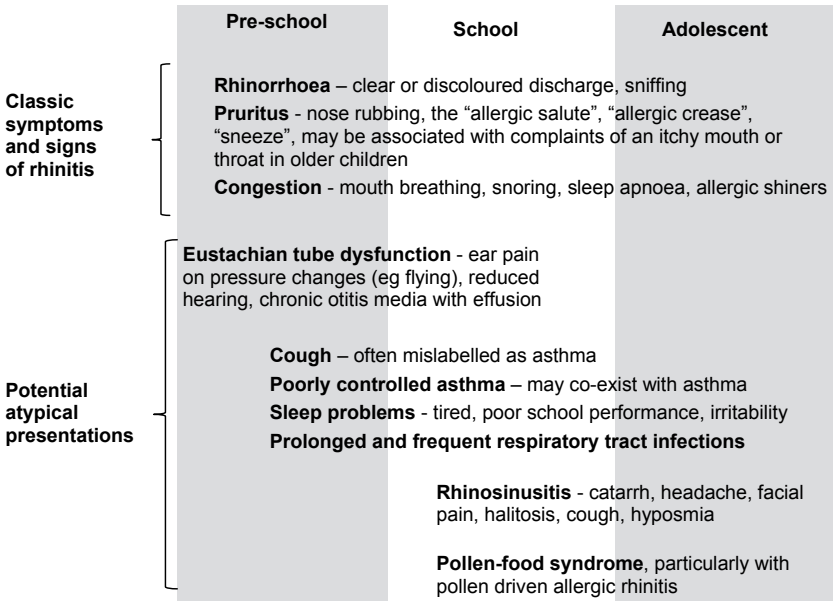

Figure 1 Recognising allergic rhinitis in childhood and adolescence. (*Reproduced with permission from Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2013;68:1102-1116, with permission from Willey Blackwell.*)

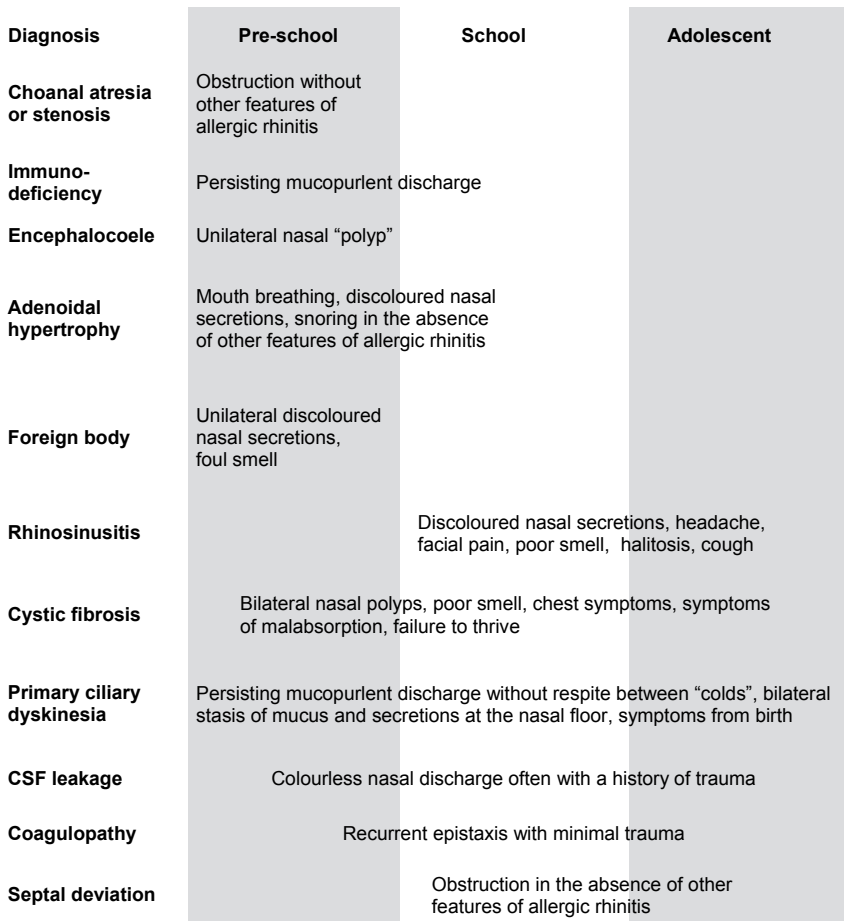

Figure 2 Differential diagnosis of allergic rhinitis in children and adolescents. (*Reproduced with permission from Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2013;68:1102-1116, with permission from Willey Blackwell.*)

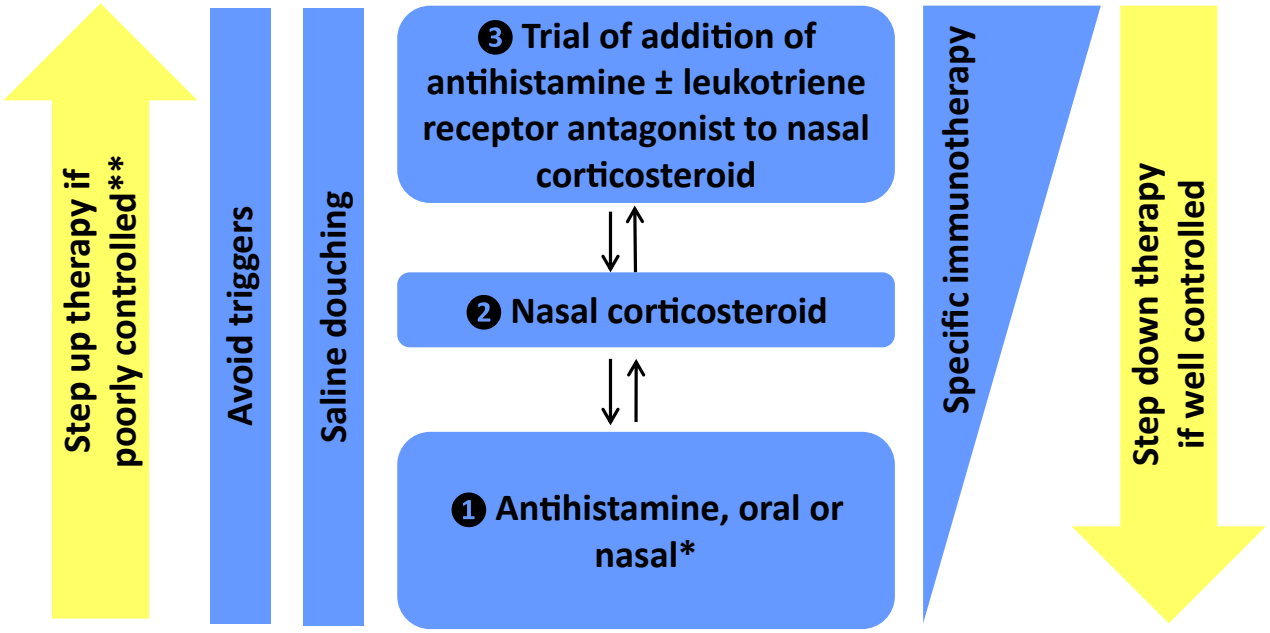

Figure 3 Approach to therapy for allergic rhinitis in children and adolescents. ❶, ❷ and ❸ are potential entry points into therapeutic approach depending on the severity of the rhinitis symptoms. For seasonal disease, regular therapy should be commenced 2 weeks before the anticipated start of symptoms. *Oral antihistamines may be better tolerated while intranasal antihistamines have a more rapid onset of action. **Reconsider diagnosis if not controlled within 1-2 weeks. If less than 2 year of age and do not respond to antihistamine within a week, reconsider diagnosis before stepping up therapy. If poorly controlled, consider a short rescue course of a decongestant or low dose oral prednisolone to gain symptom control; topical ipratropium may be useful for rhinorrhoea. (*Reproduced with permission from Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy 2013;68:1102-1116, with permission from Willey Blackwell.*)

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12 ALLERGIC RHINITIS IN ELITE ATHLETES

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KEY MESSAGES

- Rhinitis is particularly frequent in athletes and its incidence is on the increase, with symptoms occurring more often in subjects practicing swimming, cold and endurance disciplines
- Among different phenotypes described, allergic rhinitis (AR) is the most commonly observed variant
- AR often coexists with asthma and represents a risk factor for its onset
- Diagnosis is largely underestimated and should be made according to the ARIA guideline recommendations
- Special considerations should be taken into account during treatment for potential side-effects and anti-doping regulations
- Preventive measures should be undertaken to limit exposure to environmental factors that may trigger symptoms and affect performances

Rhinitis is often considered a trivial disease and is largely underdiagnosed and self-managed in athletes. However, it has been shown to significantly affect their quality-of-life and performance. The prevalence of rhinitis in athletes is particularly high and appears to be on a continuous increase (Table 1), with ranging prevalence in various studies depending on the criteria used for diagnosis. Athletes from winter, aquatic and endurance sport disciplines are more likely to have symptoms. Among different phenotypes described (vasomotor, infectious, traumatic, neutrophilic, NARES) the allergic variant is the most frequently observed. In our recent study performed in 659 Italian Olympic athletes, allergic rhinitis (AR) was found to be present in 26.2% of subjects.

Such increased occurrence has been reported to be ascribed to a global influence of the intense physical exercise on the immune system, inducing a transient immune deviation with a prevalent Th2 response, as well as to its direct trigger effect on target organs (Figure 1).

Furthermore, epidemiological data indicate that asthma and AR frequently coexist, with symptoms of rhinitis being reported in 80–90% of asthma patients, and asthma symptoms in 19–38% of those with AR. In addition, subjects with rhinitis alone often experience exercise-related airway symptoms which represent a risk factor for subsequent development of asthma. With this regard, every athlete with rhinitis should be also screened for asthma and exercise-induced bronchoconstriction according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines. The established clinical and functional assessment may also benefit of the complementary use of specific allergy questionnaires, such as the Allergy Questionnaire for Athletes (AQUA).

In addition to ARIA recommendations, special considerations should be taken into account for elite athletes for potential side-effects of some drugs, as well as to the limitations set by the World Anti-Doping Association - www.wada-ama.org - (Table 2). Inhaled and nasal steroids represent the treatment of choice, being effective in controlling inflammation and symptoms of both upper and lower airways, while reducing

TABLE 1

Prevalence of rhinitis in athletes

Study population (n)	Prevalence	Diagnostic method	Reference
Australian Olympics (185)	8.6%	Medical records analysis	Fitch, 1984
Australian Olympics (106)	7.5%	Medical records analysis	Fitch, 1984
Swiss athletes (2060)	16.8%	Questionnaire	Helbling et al, 1990
Swiss athletes (1530)	19.7%	Questionnaire	Kaelin et al, 1993
US swimmers (738)	19.0%	Questionnaire	Potts, 1996
Finish summer athletes (162)	29.6%	Skin prick tests with medical diagnosis	Helenius et al, 1998
US Olympic team (699)	16.9%	Questionnaire	Weiler et al, 1998
US winter Olympic team (196)	13.3%	Questionnaire	Weiler et al, 2000
Australian Olympic team (214)	41.0%	Skin prick tests with medical diagnosis	Katelaris et al, 2000
Italian Pre-Olympic team (265)	25.3%	Skin prick tests with medical diagnosis	Lapucci et al, 2003
Finnish Olympic athletes (446)	26.5%	Self reported medical diagnosis	Alaranta et al, 2005
Finnish marathon runners (141)	17.3%	Self reported medical diagnosis	Moreira et al, 2007
Italian preOlympics (98)	34.7%	Skin prick tests with medical diagnosis	Bonini et al, 2007
Italian Olympic athlets (659)	26.2%	Skin prick tests with medical diagnosis	Bonini et al, 2015

TABLE 2

2015 WADA international standard on drugs for treating rhinitis

Treatment	WADA rules	Notes
Inhaled steroids	Permitted	First-choice treatment
Antihistamines	Permitted	Second generation molecules should be preferred to avoid side effects
Leukotriene modifiers	Permitted	Particularly effective in subjects with concomitant asthma
Ephedrine and methylephedrine	Prohibited in competition	A concentration >10 ug/ml represents an adverse analytical finding
Immunotherapy	Permitted	SCIT should not be performed close to physical exercise

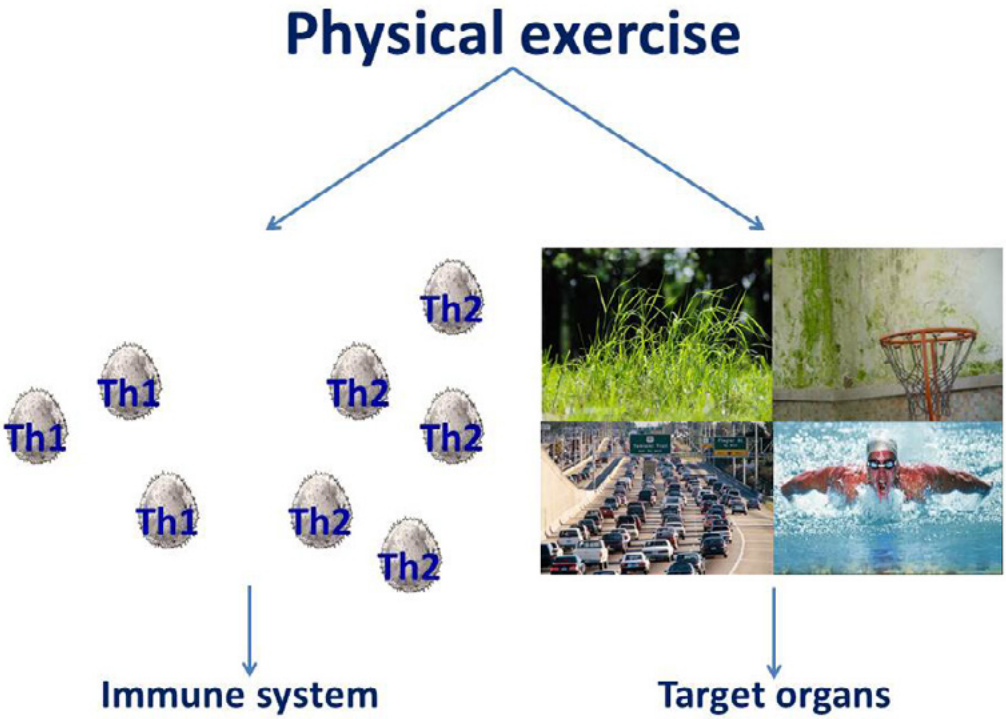

Figure 1 Effect of physical exercise on the immune system and target organs.

the need for rescue medications. Ephedrine and methylephedrine are prohibited in competition by the WADA, when their concentration in urine exceeds the allowed threshold. Although there are no restrictions for the use of antihistamines, it is well known that particularly first-generation molecules may have potential side-effects on the cardiovascular and nervous system and may induce sedation and fatigue. The use of second-generation molecules must be therefore preferred in athletes, and the potential side-effects should be carefully monitored, in relation to the relevant cardiovascular loads and the need for unaffected reaction times. Leukotriene modifiers and allergen immunotherapy are alternative effective and safe treatment strategies. Preventive measures should also be undertaken to limit exposure to environmental factors (air humidity and temperature, content in pollutants and allergens responsible for sensitization in allergic athletes) that may trigger symptoms and affect performances during training and competition. In view of this, local pollen counts and forecasts should always be made available in advance to allergic athletes, their coaches and medical staff.

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13 RHINITIS IN A TROPICAL ENVIRONMENT

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KEY MESSAGES

- Allergic rhinitis (AR) is highly prevalent in the tropics; it is often underdiagnosed and undertreated
- Major risk factors are sensitization to mites, cockroaches, moulds and pets, and less to pollens
- Economic shortages interfere with adequate care of AR patients in tropical countries
- More allergists are needed in order to meet the challenge represented by the large demand of care for AR in the tropics

In contrast to the general belief, allergies are highly prevalent in tropical countries. It is a region surrounding the Equator, limited in latitude by the Tropic of Cancer at 23° 26′ 16″ (or 23.4378°) N and the Tropic of Capricorn at 23° 26′ 16″ (or 23.4378°) S (Figure 1) with high biodiversity, variable climate, and abundant rainfall all year round with mean temperatures above 18°C. More than half of the World's population lives in the tropics.

EPIDEMIOLOGY AND RISK FACTORS

Allergic rhinitis (AR) incidence in the tropical areas is influenced by the environment, infections, and allergens. The prevalence of AR in the tropics is as high as in other regions. Anticipated protective factors, such as low hygienic conditions, do not seem to confer protection in poor communities. In Africa allergic rhinoconjunctivitis (ARC) has a prevalence between 7.2 and 27.3%. Latin America, encompassing the territories from Mexico to Paraguay and Brazil, has the greatest concentration of tropical rainforest in tropical countries, with temperatures between 20°C and 34°C, and humidity between 77 and 88%. Latin America is one of the regions with the highest prevalence of AR; according to ISAAC phase III, the prevalence is 37.6%.

Sensitization to mites constitutes the most important risk factor for AR in the tropics. Humidity facilitates the proliferation of mites and perennial exposure to high allergen concentrations. In Venezuela 97.1 % of AR patients are sensitized to mites (Table 1). In Mexico, 56% of patients are sensitized to mites, but this rate reaches 87% in tropical regions (Figure 2). Cockroach allergen sensitisation represents another risk factor. In Caracas the rate of sensitisation to cockroach allergen is 83.1%, being more common in low socioeconomic groups. Allergy to cockroaches in Latin America is likely related to availability of food, humidity and heat, poor hygiene and ventilation, and low educational levels. In the tropics there are only two seasons. Pollen concentrations are not as high as in temperate climates. Bermuda grass (*Cynodon dactylon*) hypersensitivity has been associated to seasonal exacerbations of AR in Africa, and Maize (*Zea mais*) in Zimbawe. In Caracas, *Cupressus*, *Cecropia*, *Gramineae*, *Acalypha*, *Urticaceae*, *Mimosa spp.*, *Pinus radiate*, *Ulmaceae* and *Soroceae*, *Piperaceae*, and *Eucalyptus spp*. are the pollens found in significant quantities. Mould spores are present all year round. In Venezuela sensitization rates of 56.4 to 67.4% have been reported, the most common species reported being *Aspergillus*, *Penicillium*, *Cladosporium*, *Alternaria*, and *Rhizopus*.

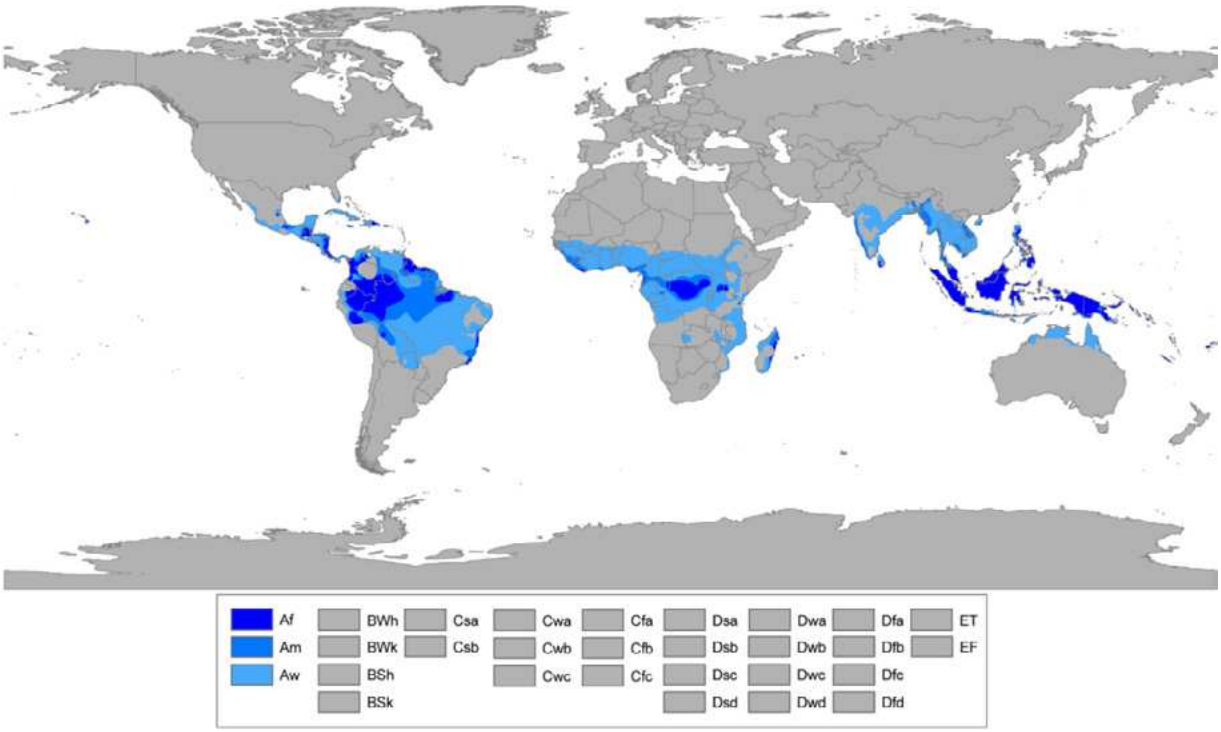

Figure 1 Tropical climate zones of the Earth where all twelve months have mean temperatures above 18°C (64°F). Peel, M. C., Finlayson, B. L., and McMahon, T. A. (University of Melbourne).

TABLE 1

Rates of Sensitization to Aeroallergens in patients with Rhinitis and Rhinosinusitis*

Allergen	% of positive skin tests
Mites	97.1
Dog	51.4
Cat	40.5
Cockroach	36.5
Moulds	22.8
Bermuda grass	21.1
Feathers	10.0
Weeds	9.8
Trees	2.9

**Modified from: Sánchez-Borges M, Fernández-Caldas E, Capriles-Hulett A, Caballero-Fonseca F. Mite hypersensitivity in patients with rhinitis and rhinosinusitis living in a tropical environment. Allergol Immunopathol (Madr). 2014; 42: 120-126.*

SOCIAL DETERMINANTS AND SOCIOECONOMIC ASPECTS IN THE TROPICS

Allergic diseases represent an important burden for health services. Although there are variations among countries, most tropical countries are poor, and patients do not have access to medical assistance. Thus, although AR is frequent in the tropics it is often underdiagnosed and undertreated. Medical management is insufficient and medications are not available or unaffordable. In many countries allergology is not recognized, or the number of allergists is low. In consequence, most patients are treated by primary care physicians. Potential risk factors for AR in this region are related

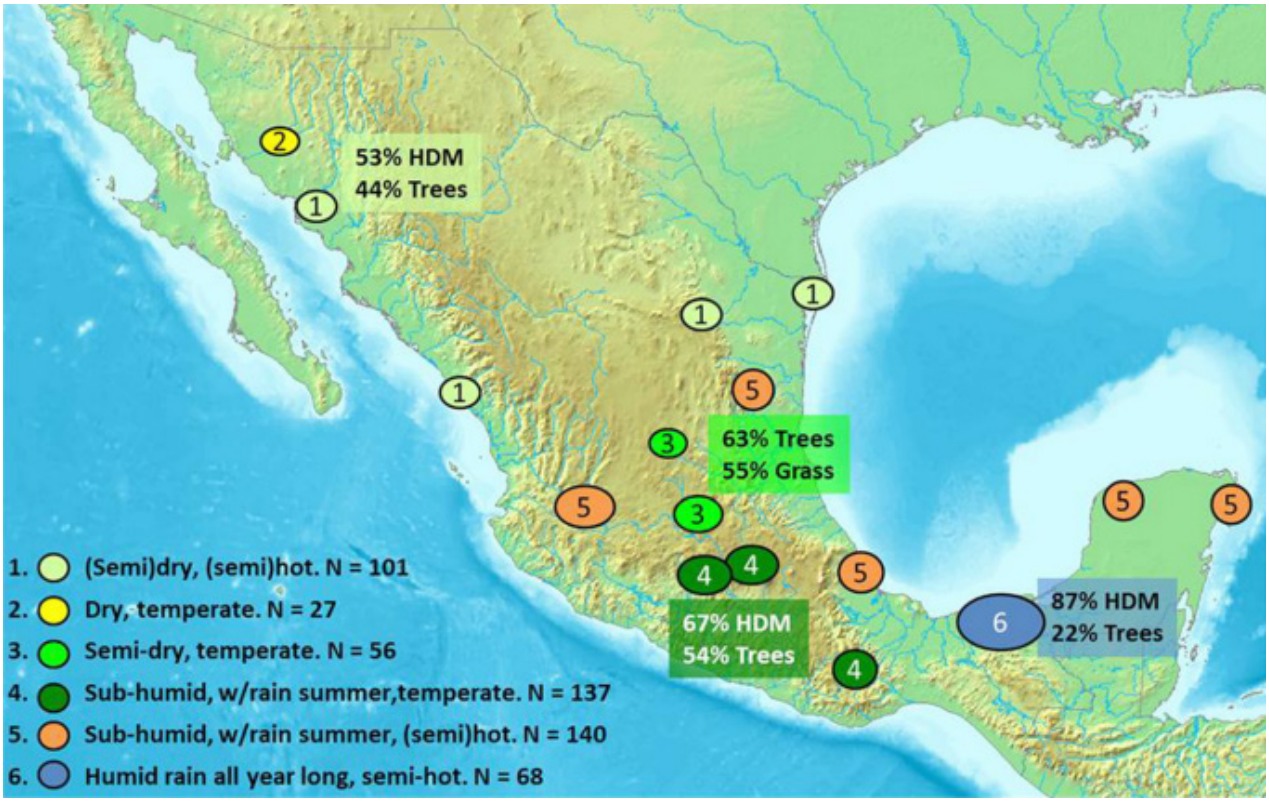

Figure 2 Allergen sensitivity throughout the Mexican Republic. (*From Larenas-Linnemann D, Michels A, Dinger H, et al. Allergen sensitization linked to climate and age, not to intermittent-persistent rhinitis in a cross-sectional cohort study in the (sub)tropics. Clin Transl Allergy. 2014;4:20.*)

to poverty, housing conditions, access to tap water, exposure to fumes, contact with animals, and large family size. In summary, weak economies and insufficient resources interfere with care for AR in tropical settings.

PREVENTION AND CONTROL

The number of patients undergoing allergy testing in the tropics is low, and the utilization of allergen immunotherapy is nearly absent. The cost of medication, dose frequency, fear of adverse effects, and low efficacy determine low treatment compliance. A higher number of physicians trained in allergology are needed in order to meet the increasing demand.

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14 SEVERITY AND CONTROL IN ALLERGIC RHINITIS

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KEY MESSAGES

- Guidelines for allergic rhinitis (AR) management are based on symptom severity assessed by simple questions regarding their impact on quality of life
- The management of AR should rather be based on control; new disease control-defined paradigms are emerging
- There is currently no single and universally accepted definition of AR control
- Control tools should include objective and subjective measurements of symptoms and their impact on daily activities

In order to enhance the effectiveness and quality of management for allergic rhinitis (AR), a number of international guidelines and consensus statements have been developed and regularly adapted over the past two decades. The Allergic Rhinitis and its Impact on Asthma (ARIA) was the first evidence-based guidelines, proposed in conjunction with the World Health Organization. It focuses on the assessment and treatment of AR based on severity as assessed by simple quality of life (QoL) measurements. Although the treatment guidelines are now well established, treated patients may report poor levels of satisfaction and continue to be undertreated and at risk for acute exacerbations, resulting in reduced productivity at work, school performance and QoL, triggering increased healthcare costs and the use of oral corticosteroids. The level of AR' control is often overestimated by both patients and physicians, resulting in failure to make the necessary adjustments to medication. Thus, a measure of AR control should be used to evaluate treatment outcomes and simplify monitoring. As implement for asthma management by the the Global Initiative for Asthma (GINA) guidelines, the generalization of the term "control" is now being considered for the management of patients with AR, chronic rhinosinusitis, chronic urticaria and atopic dermatitis.

There is currently no single definition of AR control, since its determination depends on the variables taken into account by the different available tools. As a consequence, there is no universally agreed indication that AR control should be measured directly. Rhinitis control is essentially "absence of symptoms". Most of the control tools developed so far focus on objective and subjective measurements of daily or nocturnal nasal and ocular symptoms (congestion, rhinorrhea, sneezing, pruritus, post-nasal drip), symptom magnitude (i.e., the patients' perception of how bothersome their symptoms are), patient-reported metrics of QoL (i.e., impairment in sleep or daily activities) and satisfaction, and some objective measurements (e.g., peak nasal inspiratory flow, rhinomanometry, increased use of rescue medication). Many instruments, such as The Control of Allergic Rhinitis and Asthma Test (CARAT), Rhinitis Control Assessment Test (RCAT), The Allergic Rhinitis Control Test (ARCT), a Visual Analog Scale (VAS) and other new questionnaires requiring validation have appeared and have been used in the assessment of the patient's clinical symptoms (Table 1). New approaches based on disease control are now emerging (Figure 1). They will need to be evaluated prospectively.

Immunotherapy			
Environmental control			
Control medication steps			
1	**2**	**3**	**4 (Specialist care only)**
One of: • Oral antihistamine • Intranasal antihistamine • Intranasal cromolyn/ nedocromyl • Leukotriene receptor antagonist	**One of:** • Intranasal corticosteroid (***preferred***) • Oral antihistamine • Intranasal antihistamine • Leukotriene receptor antagonist	***Combination of Intranasal corticosteroids*** **with one or more of *:** • Intranasal antihistamine • Oral antihistamine • Leukotriene receptor antagonist	Consider omalizumab *(not approved for rhinitis)* Consider surgical treatment of concurrent pathology
Rescue medication			
• Decongestants (oral/intranasal) • Anticholinergics (Intranasal)			• Oral corticosteroids
Reassess diagnosis and/or adherence and evaluate potential comorbidities and/or anatomic abnormalities prior to considering step-up**			

**There is little evidence of additional efficacy of these drugs to intranasal corticosteroids.*

*** Step up is indicated if symptoms remain uncontrolled and step down if control is achieved with the employed regimen. Although the control principle may be valid for other rhinitis phenotypes as well, specific medications should be adjusted accordingly.*

Figure 1 New proposal to manage allergic rhinitis based on control. (*Reproduced with permission from Papadopoulos NG, Bernstein JA, Demoly P, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. Allergy 2015;70:474-494, with permission from Willey Blackwell.*)

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TABLE 1

A comparison of three published allergic rhinitis control questionnaires

	The Control of Allergic Rhinitis and Asthma Test (CARAT)	The Rhinitis Control Assessment Test (RCAT)	The Allergic Rhinitis Control Test (ARCT)
Administration mode	self-questionnaire	self-questionnaire	self-questionnaire
Diseases considered	allergic rhinitis and asthma	allergic rhinitis	allergic rhinitis
Period of evaluation	The previous 4 weeks	The- previous week	The previous 2 weeks
Number of final items/questions	17 in development 10 in the final tool	26 in development 6 in the final tool	5 in the final tool
Response type	4-point frequency scale and some yes/no items	5-point Likert scale	5-point frequency scale
Validation status	Tested in 141 non-treated adult patients (CARAT17) and then 193 adults (CARAT10). Internal consistency over 0.70. Longitudinal validation underway	Psychometric validation by 410 patients consulting allergy specialists. God psychometric properties and reliable internal consistency (Cronbach alpha coefficient: 0.70)	Tested in 902 patients selected by 411 primary care physicians and allergists. Internal consistency: 0.77
Other comments	Tested in patients consulting an allergist	Significant correlations with physician-rated disease severity, total nasal symptom score and physician-recommended change in therapy	Based on the Asthma Control Questionnaire. Significant correlations with the clinical picture and the impact of allergic rhinitis on social and sports activities

(From Demoly P1, Calderon MA, Casale T, et al. Assessment of disease control in allergic rhinitis. Clin Transl Allergy. 2013;3:7; Reprinted with permission under the Creative Common Attribution License or equivalent.)

15 PHENOTYPES AND ENDOTYPES OF ALLERGIC RHINITIS

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KEY MESSAGES

- Better management of allergic diseases needs a sharpened understanding of disease heterogeneity and mechanisms in relation to clinically significant outcomes
- Phenotypes describing observable clinical and morphologic characteristics and unique responses to treatment have been developed; however they do not relate to disease mechanisms
- Recently, extended heterogeneous and disease-related metabolic, inflammatory, immunological, and remodeling pathways have been described, and reproducible patterns are defined as disease endotypes
- An endotype might consist of several intricated mechanisms that cannot be clearly separated into "pure single molecular mechanism" thus being a "complex endotype"
- The Th2 type inflammation or aspirin exacerbated respiratory disease can be defined as complex endotypes
- The description of an endotype relies on biomarkers, which can be the signature of a complex underlying pathway or a key-molecule for a role in a particular disease endotype

PHENOTYPES AND ENDOTYPES

The heterogeneity of allergic diseases in relation to clinically significant outcomes, including response to treatment has been established beyond any doubt. At first, phenotypes describing clinical and morphologic characteristics as well as unique responses to treatment have been developed to address the complexities of the disease. Several allergic rhinitis (AR) phenotypes can be described based on the predominant symptom ("runners" vs. "blockers"), occurrence of symptoms ("seasonal" vs "perennial" or "intermittent" versus "persistent"), pattern of sensitisation ("mono-" vs. "polysensitised") severity or response to treatment. The phenotype driven approach of AR is already in place for many years and acknowledged by the international guidelines such as ARIA, since we tend to use as first line treatment nasal steroids for blockers and antihistamines or anticholinergics for runners, and we treat AR according to its severity. Even the elicitation of symptoms can separate different clusters of AR patients: for example the aeroallergen challenge chamber (ACC) exposure dichotomises patients into low versus high level of symptoms developing slow or fast while natural exposure versus ACC divides patients into concordant responders to both type of exposure or discordant responders, with a greater symptom score in the natural season.

Phenotypes may be clinically relevant in terms of presentation, triggers, and treatment response, but do not necessarily relate to or give insights into the underlying pathological mechanism. For example, the recently described local allergic rhinitis is certainly an interesting AR phenotype posing several questions on the mechanisms involved in the lack of systemic atopy. For most of the allergic diseases extended heterogeneous disease-related inflammatory, immunological, and metabolic pathways have been described, and a reproducible underlying mechanism is defined as a disease endotype. Classifying

AR based on underlying pathophysiologic mechanisms, known as endotyping, offers a stratified approach for a better assessment of disease' epidemiology, genetic background and environmental risk factors, for the development of new targeted therapies and for a better selection of responders to targeted treatment.

To become clinically relevant, the endotype should be related to validated biomarkers that correspond to the underlying mechanism. The purpose of the biomarker is to identify disease endotype, predict onset and prognosis of a disease, measure exposure, monitor response to treatment and forecast unfavourable evolution. The biomarker can be the signature of a complex underlying pathway or a key-molecule of a particular disease endotype. To further complicate the picture, the predictive value of the same biomarker is highly variable across age groups, disease severity and in relation to the outcome. The ideal biomarker should be pathway-specific, reproducible in the same individual and in an independent prediction cohort and usable as a diagnostic test (easily measurable and affordable). New strategies for discovery and validation of biomarkers such as gene expression (microarrays) and omics provide combined signatures as per systems medicine.

THE CONCEPT OF COMPLEX ENDOTYPES

Allergic diseases, such as asthma, AR or atopic dermatitis, manifest as heterogeneous syndromes that cover a broad spectrum of complex genetic, inflammatory, metabolic and remodelling networks that lead to several pathogenetic pathways. Single molecular mechanism-linked endotypes can be defined for an allergic disease, however most allergic endotypes involve concomitantly several pathways. Examples of such complex endotypes are Th2 inflammation or aspirin-exacerbated respiratory disease.

THE TYPE 2 COMPLEX ENDOTYPE

The type 2 complex endotype in allergic diseases includes innate lymphoid cells, T helper 2 cells, tissue eosinophilia and systemic and local IgE production. The IL-9/mast cell/PGD2 pathway activation, Th1 or Th17 cells may add to the Th2-driven inflammation, with their role in apoptosis of the epithelium (Th1) and in promoting neutrophilic inflammation (Th17). Further influences may be added by the associated microbiota (superantigens) or by activation of peculiar metabolic pathways such as the eicosanoid pathway in aspirin-exacerbated respiratory disease or the L-Arg/ADMA or the lectin pathway in obesity (Figure 1).

The type 2 inflammation is characterized by a high cellular plasticity that enables the cells to adapt to a specific inflammatory milieu. Innate cytokines such as IL-33 and TSLP modulate the mast cell phenotype, while type 2 cytokines influence permissiveness of epithelium for allergens and of the endothelium for the recruitment of inflammatory cells to inflamed tissues and are involved in the production of mucus.

The "Holy Grail" of endotyping is to pinpoint the essential nodes of the network that are unique for one endotype and relate to relevant clinical end-points such as disease severity or response to treatment. For Type 2 inflammation endotype, three such nodes can be described, each depicting a distinct subendotype: the IL-5 pathway, the IL-4/IL-13 pathway and the IgE pathway (Figure 1). These pathways can be demonstrated for allergic asthma, where targeted intervention and the fast development of biomarkers allow such a separation. Since for AR the targeted treatment has not been fully developed one can just assume that given the similarities between the Th2-driven inflammation in the nasal and the bronchial mucosa and the well established systemic link between AR and asthma, the Th2 nasal endotype to behave similar to asthma. In addition, the well recognized link between rhinitis and asthma should be integrated and tackled within the framework provided by endotypes.

Several biomarkers for Type 2 type inflammation have been described (Table 1). Each biomarker reflects a compartment or a pathway involved in type 2 inflammation, related to Th2 cells and ILC2. For non-specific interventions, such as topical corticosteroids, all described biomarkers can be used to predict response. However, for more targeted interventions, such as anti-IL-5 or anti-IL-13, each of these Th2 or ILC2 biomarkers needs to be related to the specifically targeted pathway.

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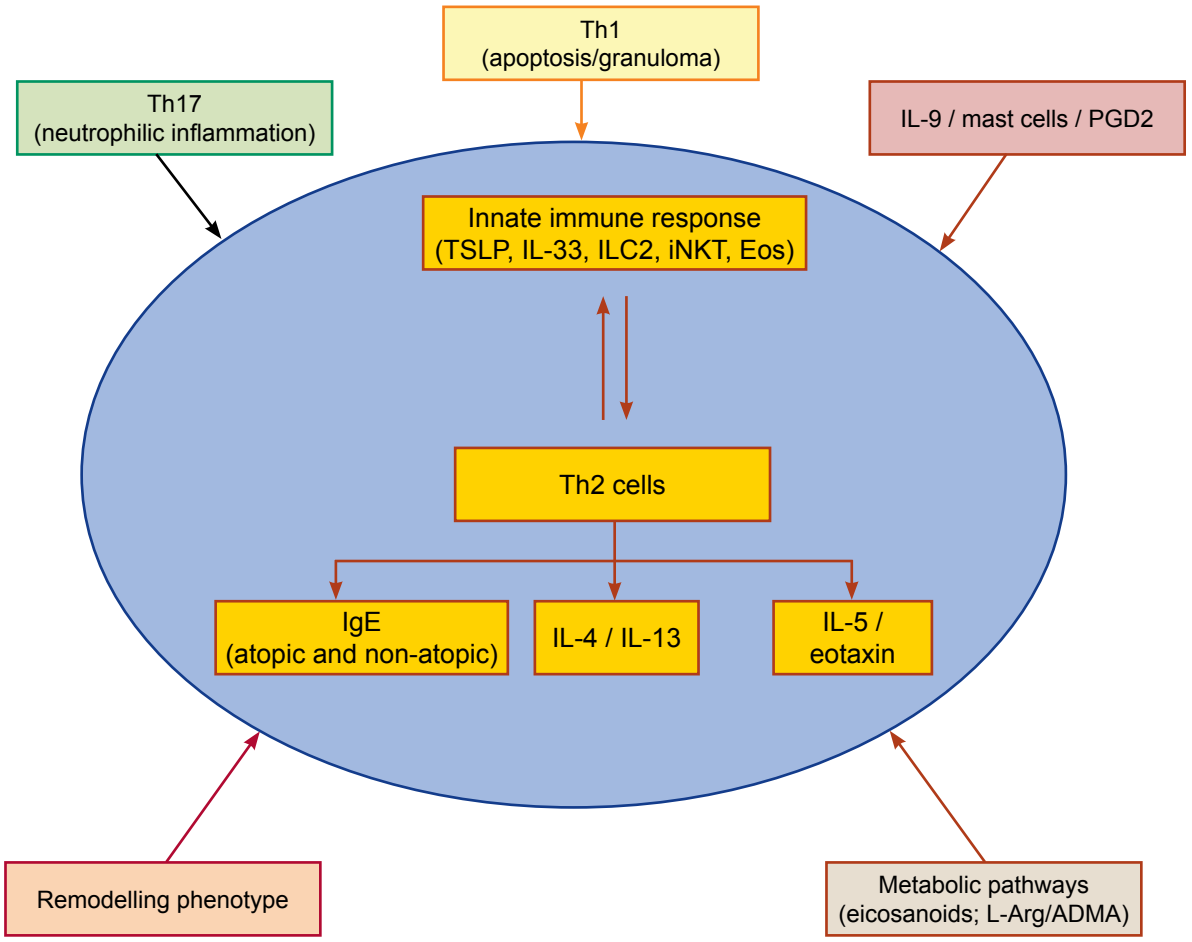

Figure 1 The complex network of Type 2 endotype in allergic diseases involves the interaction between innate immune response and Th2 cells. Three major downstream effector pathways can be described: the IgE pathway, the IL-5/eotaxin pathway, and the IL- 4/IL-13 pathway. Additional modulators of the Th2 endotype can be described such as the IL-9/ mast cell axis, Th17 or Th1 cells, activation of the metabolic pathways (*Reproduced with permission from Agache I, Sugita K, Morita H, et al. The Complex Type 2 Endotype in Allergy and Asthma: From Laboratory to Bedside. Curr Allergy Asthma Rep. 2015, in press.*)

TABLE 1

Type 2 inflammation biomarkers in allergic diseases

Biomarker	Clinical Utility	Reproducibility
Nasal eosinophils	Clinical setting	?
Blood eosinophils	Clinical setting	No
Serum periostin	Research setting	Yes
The Th2 gene signature (serpin B2, periostin, CLCA1 or CLC, CPA3, DNA- SE1L3) in nasal epithelial cells	Research setting	Yes
The salivary inflammatory profile.	Research setting	?

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16 THE BURDEN OF ALLERGIC RHINITIS ON PATIENTS' QUALITY OF LIFE

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KEY MESSAGES

- Allergic rhinitis (AR) is a systemic disease affecting not only the nasal function, but general well-being as well (hay 'fever')
- Patients frequently consider their condition as being part of how they are, without seeking medical attention
- Automedication is common in patients with AR, resulting in adverse effects such as sedation from first generation antihistamines and rhinitis medicamentosa from misuse of topical vasoconstrictors
- As a chronic condition AR puts a considerable economic burden on sufferers
- Allergen immunotherapy, subcutaneous or sublingual, can improve quality of life and reduce the economic burden of AR

Allergic rhinitis (AR) is often considered a local condition caused by an allergic reaction to inhalant allergens in the nose. However, in patients suffering from AR apart from local immunologic changes, also a deviation of the systemic immune response has been documented. During allergen exposure serum levels of specific IgE, eosinophil-derived proteases and cytokines are all elevated. These are probably the cause of the feverish feeling and tiredness expressed by several patients, leading in the past to the term hay-fever.

AR patients often accept their condition as being part of how they are and as such do not seek medical attention. Even less often advice from a specialist is sought. It is common that patients refer after they have suffered from symptoms for years, before visiting the physician. During peaks of symptoms the burden of self-medication is frequent, often in the form of first generation antihistamines, alone or in a cold-mix. When the main symptom is nasal obstruction, the mostly used over the counter (OTC) medication is a topical vasoconstrictor.

As such, AR affects the patient's well-being in several ways (Figure 1). Firstly, the local nasal conditions such as rhinorrhea, sneezing and pruritus are bothersome and can interfere with the social functioning of sufferers. At night, nasal obstruction reduces the quality of sleep and causes odynophagia in the morning, because of nocturnal oral respiration. Secondly, the systemic immunologic reactions give the patient a feeling of malaise and unwell being and in some cases even arthralgia has been documented, especially in children. Thirdly, side effects of the OTC, self-prescribed medication poses more burden on the AR patient. The sedative effect of first generation antihistamines can have deleterious consequences, because it not only reduces school and work performance, but intake of first generation antihistamines has even been linked to car and plane accidents. Misuse of topical decongestants in nasal sprays easily leads to a rebound nasal obstruction and finally rhinitis medicamentosa.

Measuring quality of life in patients with allergic rhinitis has to take into account all these different aspects. As such, a generic health-related quality of life questionnaire might not be the ideal instrument. Specific rhinitis, rhinoconjunctivitis and rhinosinusitis quality of life questionnaires have

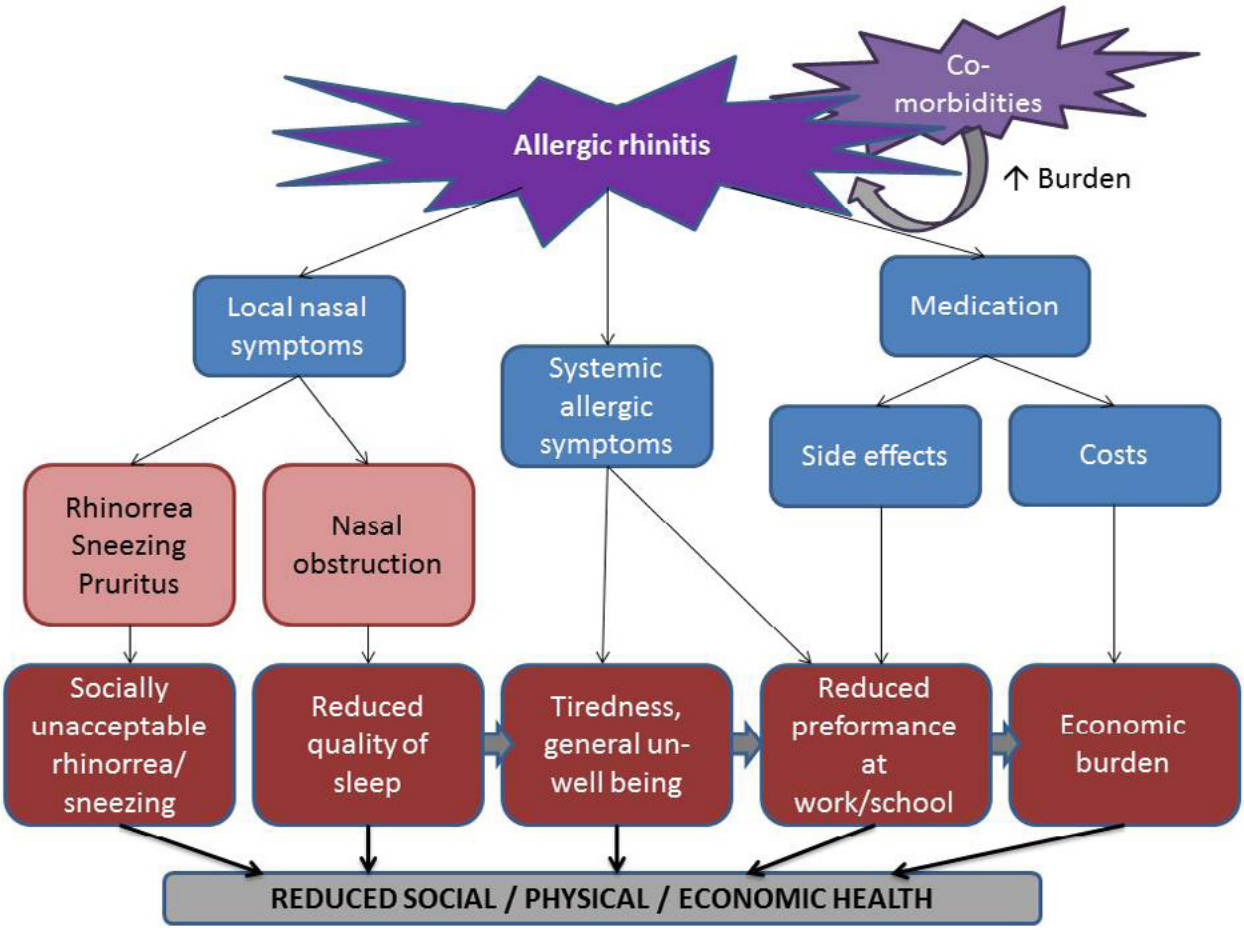

Figure 1 The complex interplay of factors decreasing quality of life in patients with allergic rhinitis.

TABLE 1

Mesuring disease burden of allergic rhinoconjunctivitis (ARC): Issues to be taken into account for selection of patient-related outcomes		
The phenotype of ARC being treated	seasonal and perennial ARC	seasonality, timing of exposure
Age of the patients	Adult Pediatric	Pediatric patients: caretaker bias
The nature of the intervention being evaluated	Pharmacotherapy AIT	For AITthe effect should be measured after a longer time interval
Symptoms beyond ARC	Asthma, otitis media with efffusion, sinusitis	Symptoms of the co-morbidity included in the questionnaire (eg RhinAsthma)

been developed for adults, adolescents and children, e.g. the RQLQ. To select the best instrument, several issues have to be considered (Table 1).

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17 ADHERENCE TO THE MANAGEMENT PLAN OF ALLERGIC RHINITIS

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KEY MESSAGES

- More than 50% of patients with allergic rhinitis (AR) do not fulfill their prescription. Many factors may negatively account for patient adherence to treatment
- Adherence is a multidimensional phenomenon determined by the interplay of different factors. Hence, it is a dynamic process that varies over treatment duration
- Targeted management plans, based on patient's characteristics, symptoms, co-morbid conditions, and preferences, may increase adherence and patients' perception of symptom relief
- Education is a key factor in promoting adherence and providing the best care for the patients with AR. Additional research to determine the best methods for education delivery is needed

Currently, management plan of allergic rhinitis (AR) includes allergen avoidance, pharmacotherapy, allergen immunotherapy (AIT) and patient's education. The management of AR, same as many chronic diseases, is affected by the adherence issues, since at least one-third of patients may be non-adherent to their AR treatment regimen, and 40-80% of patients may discontinue the treatment after the first 6 weeks. Adherence is a multidimensional phenomenon, currently measured by variable methods. Figure 1 summarizes five dimensions of determinants for adherence, which may have also relevance for AR.

There are very few data on the adherence to allergen avoidance measures, available only for house dust mites and indicating a great adherence rate, when encasings are provided without costs. In clinical trials involving both pharmacological treatments and AIT, where patients are strictly monitored, the adherence is obviously much better compared to real life studies. Thus, for antihistamines, clinical trials report an overall long-term adherence of about 80%, whereas real-life studies suggest a rate of less than 50%, with one third of patients adapting or modifying the prescribed treatment. An easy schedule and different drug formulation as well as safety issues should be taken into consideration. For intranasal steroids (INS), low efficacy perception and bothersome adverse effects contribute to lack of satisfaction with treatment and discontinuation of treatment in AR patients. The compliance has been formally assessed mainly on the basis of patient's preference (i.e. INS smell, taste, type of formulation), the preference being inversely correlated to the intensity of the sensorial attributes. The rate of adherence to AIT is currently low. Multiple predictors of non-adherence have been identified, in particular the inconvenience and the occurrence of side effects for subcutaneous AIT, while the perceived (vs. expected) efficacy and the costs seem to play a major role for the adherence to sublingual AIT. The reasons for non-adherence might differ between children and adults (Table 1).

Therefore, the approach to AR management must be individualized, considering many variable factors, such as patients' age, frequency and severity of symptoms, degree of impairment of QOL, patient preferences, response, tolerability and compliance to previous medications, presence of co-morbidities and costs. An ef-

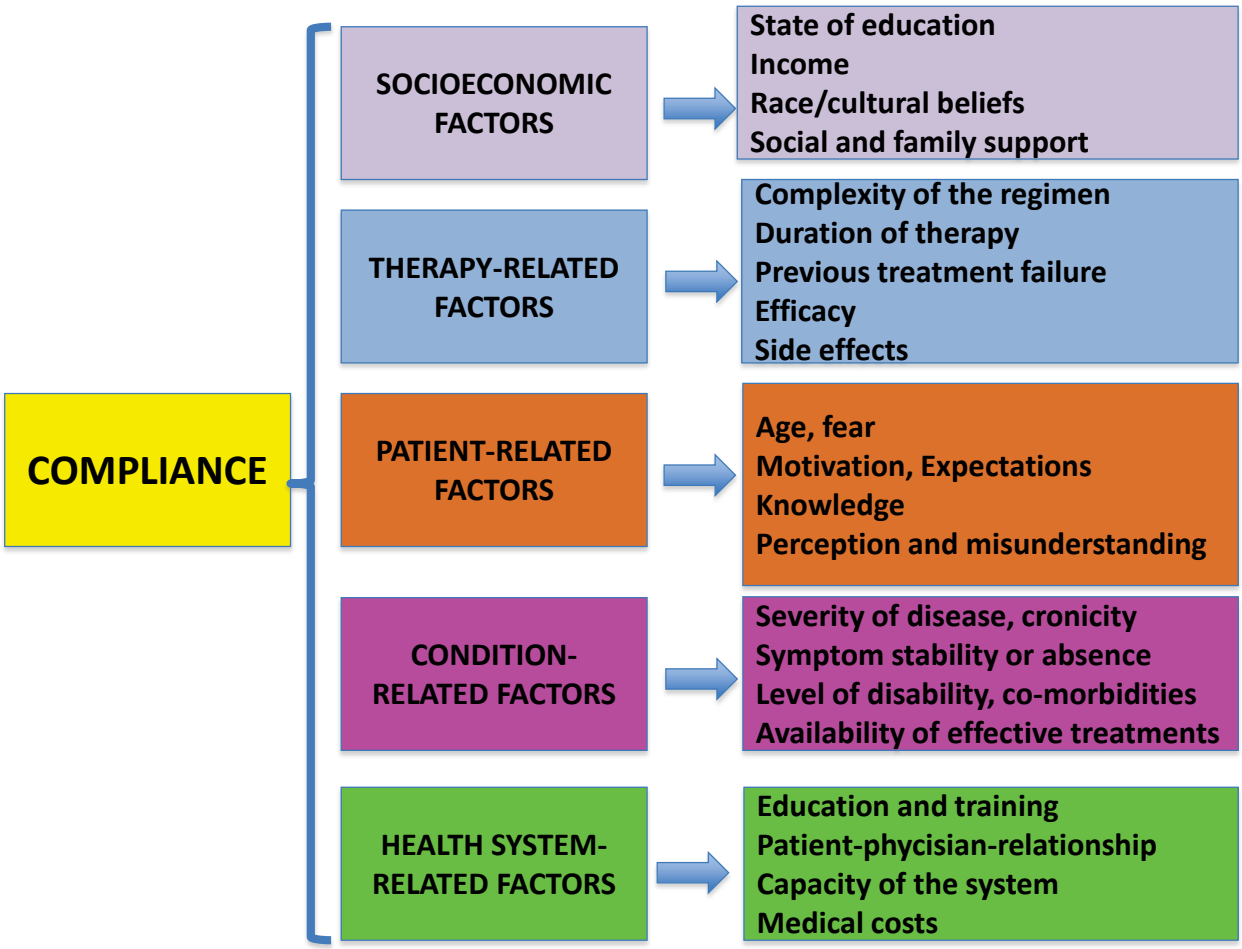

Figure 1 Dimensions of adherence. (*Modified from Sabaté E. World Health Organization. Adherence to long-term therapies: evidence for action. Switzerland: World Health Organization; 2003.*)

fective AR management requires the development of a doctor/patient/family partnership and tailored patient and family education. In some studies, a structured educational programme has resulted in enhanced adherence to AR treatment and follow-up care, improved patients' perception of symptom relief, and decrease in prescribed medications.

Although there is a general agreement that education is a key element, the best delivery method, frequency, and educational setting are still not established.

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TABLE 1

Some common reasons for poor adherence to management plan in patients with allergic rhinitis*
ADULTS:
Feeling that the drug does not have a rapid-onset and long-lasting effect (drugs not effective)
Belief that the medication is no longer needed
Belief that medication is only needed intermittently or when symptoms are noticeable
Forget to take the medication
Fear of side effects
Inconvenience (complexity of the therapeutic regimen)
Difficulty taking the medication
Cost
CHILDREN:
Difficulty to take the medication
Do not want to feel different from other children (particularly at school)
Fear of side effects (both child and parents)
Division of responsibility for treatment between child, school personnel, parents, and other caregivers

** Modified from Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. Otolaryngol Head Neck Surg 2007;136:S107-124.*

18 ILLNESS PERCEPTION, MOOD AND COPING IN PATIENTS WITH RHINITIS

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KEY MESSAGES

- Rhinitis can be associated with significant psychological and social burden
- How patients perceive their rhinitis can differ widely and often challenges the understanding of the disease by professionals
- Adopting a bio-psychosocial approach in the consultation ensures that the wider impacts of rhinitis are recognised, and can then be taken into account when advising and prescribing
- Patient's perceptions about their rhinitis appear to be independent of the severity and persistence of their disease, this may lead to under-diagnosis and under-treatment

ILLNESS PERCEPTIONS

Health psychologists have developed models to help us understand how patient's perceptions about their illness links to the way they behave (e.g. self-care, medication adherence). A widely used model is the Leventhal's Common Sense Model of self-regulation, which provides a framework for understanding how symptom-based and psychological factors combine to form patient's own model of illness, and how this in turn influences their coping strategies and outcomes. The model, developed in 1984, has been applied to many chronic illnesses (Figure 1), but only recently in rhinitis. One British study of adults with seasonal allergic rhinitis (AR) found two distinct groups of patients, those with negative beliefs about hay fever and its treatment (approximately 40%), and those with more positive beliefs. Those with negative beliefs perceived control of their illness as minimal and their treatment ineffective.

Eliciting patients' beliefs during the consultation can reveal assumptions that differ from those of the clinician and these patient perceptions need to be considered when negotiating treatment plans. Interestingly, a recent Italian study found patient perceptions to be independent of severity or persistence of rhinitis. The authors suggested this may explain why AR is under-diagnosed and undertreated, even in its most severe forms.

COPING

Patients with rhinitis have to deal with multiple challenges; the feelings of having the disease (such as disappointment or anger), the symptoms of rhinitis, the need and costs of seeking health care and the inconvenience and side-effects of treatment. From the general literature it is known that patients cope with adversity in numerous ways, ranging from the passive (e.g. acceptance, disengagement) through to very active strategies, for example use of support (e.g. social, religious). Coping can be measured with validated questionnaires and in Braido's study the most frequently used coping mechanisms were positive reinterpretation, taking action, planning, use of social support and acceptance. These coping mechanisms can all be encouraged in the consultation (Table 1).

MOOD

Superficially rhinitis may be seen as a solely physical disorder; however it is well documented that it also impacts on psychological wellbeing, sometimes referred to as the "allergy blues". Rhinitis

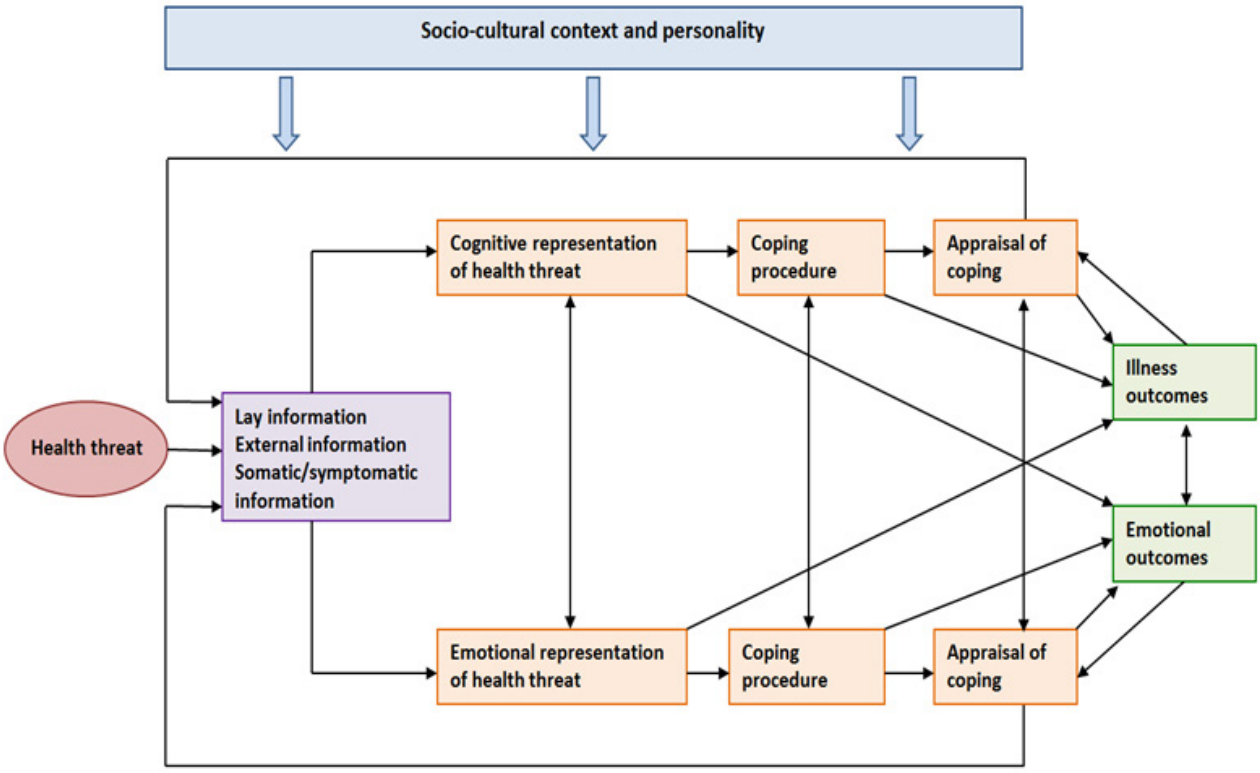

Figure 1 Leventhal's Common Sense Model. This model is often used as a framework for examining individuals' beliefs about their illness and health behaviours. Leventhal suggested that patients form beliefs about their illness (*cognitive representations*) and emotional responses (*emotional representations*) to their illness and together these influence their coping strategies. The processing of the information feeds back, modifying the patient's beliefs and coping mechanisms.

TABLE 1

Tips for helping patients cope with their rhinitis
• Learn to accept your illness – acceptance is often the starting point for action, individuals are then better placed to move on, to plan, to seek support and do the things that can improve their quality of life
• Take action and be involved in your treatment – impact can be reduced by becoming actively involved in your care and establishing a good rapport with your health carers
• Planning - this can relate to avoiding the triggers and also planning the actions you want to take
• Seeking support – seek assistance, information and advice on what to do. Sources of advice are plentiful (e.g. books, internet, patient support groups)
• Reinterpretation of the situation – this is about viewing your rhinitis in a more positive light and looking for benefits in your situation (e.g. the things you have learnt or the people you have met).

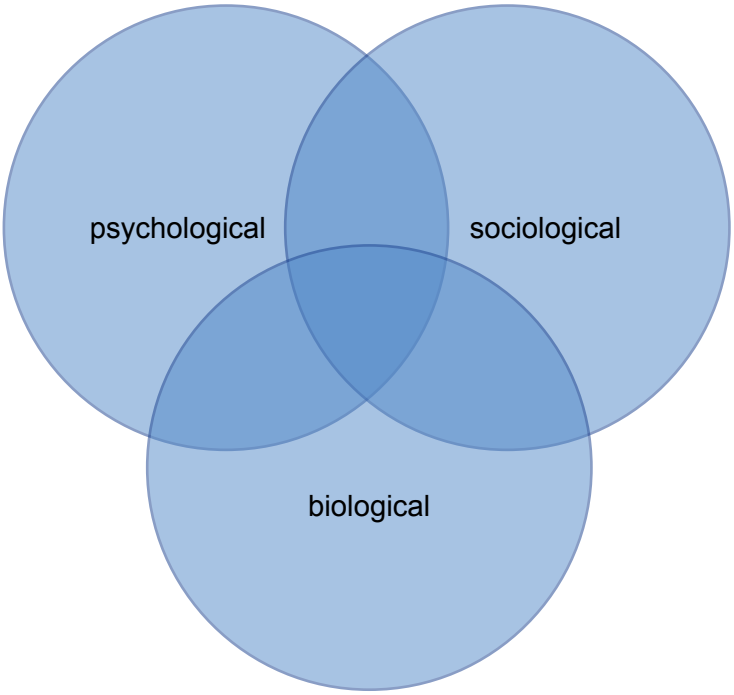

Figure 2 Bio-psychosocial model of health and illness. Psychosocial factors, including beliefs, relationships and mood, impact on patient's quality of life and ability to cope with their illness. Incorporating a holistic view in the consultation can ensure patient's wellbeing is addressed in its entirety.

can interfere with sleep, and this can cause poor concentration and depression. There may also be a biological explanation; interest in this area was triggered by the observation that high tree pollen levels correlated with increased suicide rates. It has been hypothesised that it is the cytokine released which affects brain function, triggering sadness, malaise, poor concentration, and increased sleepiness. This association requires further exploration, but it supports the need to adopt a holistic approach (Figure 2), when managing patients with rhinitis, and being attentive to their mood and psychological well-being, referring the patient to a mental health professional for evaluation if appropriate.

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19 PHARMACOECONOMICS OF ALLERGIC RHINITIS

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KEY MESSAGES

- Allergic rhinitis (AR) is a common, chronic illness with a long duration of disease activity that can require many years of treatment
- AR is associated with considerable direct and indirect costs to the patient and healthcare system
- Poorly controlled AR can be associated with comorbid illnesses that can compound treatment costs, such as asthma or sinusitis
- In contrast to pharmacotherapy, allergen immunotherapy (AIT) can provide long-term clinical benefits after discontinuation. The sustained benefits of AIT can translate into significant cost-savings over time
- Two systematic reviews concluded that both the sublingual and the subcutaneous routes for AIT delivery are cost-effective compared with standard drug treatment with no strong evidence favoring a particular route
- The cost-effective time point was about 6 years after AIT initiation in one systematic review, but as early as 3 months in large retrospective claims analyses studies

Allergic respiratory diseases represent some of the most common and costliest chronic conditions worldwide. Global estimates suggest that allergic rhinitis (AR) affects approximately 500 million people, with higher prevalence in westernized countries. Approximately 113 million people in Europe and 30 to 60 million in the United States (US) are affected by AR. Studies comparing AR prevalence in patient-reported questionnaires with subsequent clinically-confirmed AR, suggest AR is frequently underdiagnosed, often undertreated, and/or poorly controlled. In addition to significant patient discomfort, AR can be associated with a number of 'secondary' symptoms and comorbid conditions, such as asthma, presenteeism, impaired sleep with subsequent daytime fatigue, otitis media, and sinusitis that significantly impair quality of life, and increase the direct and indirect costs of AR.

The total indirect costs associated with AR can be considerable and may actually be greater than the direct costs. In addition to over-the-counter medications, indirect costs include lost work productivity. The annual loss to employers related to untreated AR-related presenteeism has been estimated to be approximately €100 billion in Europe (2011 value). In a survey of U.S. employees, the total annual cost of lost productivity attributable to AR was significantly higher than the cost for any other condition assessed including diabetes and coronary heart disease.

There are a number of secondary outcomes assessed in randomized, controlled trials such as impact on quality of life via a validated questionnaire, but few studies directly assess economic outcomes. Cost comparisons can only be estimated by translating medication scores (use) and the secondary clinical outcomes reported (e.g., hospitalizations, or unscheduled clinic or emergency visits) into actual costs based on the reimbursement fees of that particular healthcare system. Another limitation is that many do

TABLE 1

Systematic reviews evaluating allergen immunotherapy health economics

Author (Number of studies included in economic analyses)	Inclusion criteria	Economic outcome	SCIT vs SDT	SLIT tablets vs, SDT	SLIT drops vs SDT,	SCIT vs, SLIT vs SDT
Meadows 2013 (14)	All included EEs critically appraised using Cochrane Collaboration checklists	Both SCIT and SLIT may be cost-effective from around 6 years	6 Cost-effective from 3, 6 and 10 but varied with perspective	3 Cost-effective at ~ 6 years and various ICER	2 All favored SLIT	3 SCIT more cost-effective over time
Hankin 2014 (24)	SR of Medline studies reporting health economic outcomes associated with AIT.	23 favored AIT over SDT	10 All favored SCIT	8 1 found higher costs with SLIT	1 reduced costs by year 4	4 All favored SLIT SLIT 48% cost-savings from HCS perspective

SCIT=subcutaneous allergy immunotherapy; SLIT=sublingual allergy immunotherapy; SDT=standard drug treatment, EE=economic evaluations, SR =systematic review

** included 3 studies that evaluated the actual total healthcare cost via claims analyses not included in the Meadows review*

Adapted with permission from Cox L. Allergy immunotherapy in reducing healthcare cost. Curr Opin Otolaryngol Head Neck Surg 2015;23:247-254.

not provide outcome information related to comorbid illnesses or the indirect costs of AR (e.g., last work days).

The management of AR is multifaceted and may include avoidance measures, pharmacotherapy, and allergen immunotherapy (AIT). Multiple controlled-trials and systematic reviews indicate the magnitude of AIT clinical efficacy is generally superior to pharmacotherapy, with only nasal corticosteroids approaching the 20 to 30 percent improvement over placebo seen in most AIT trials. An additional consideration when evaluating the pharmacoeconomic of AR, is that allergy medications provide no sustained benefits after discontinuation. In contrast, AIT can provide symptomatic improvement during and years after discontinuation. Additionally, AIT may prevent the progression of the allergic rhinitis to asthma, which is a considerably more 'expensive' disease in terms of both costs and morbidity.

The economic benefit of AIT over standard drug treatment (SDT) has been confirmed from several different perspectives; societal, healthcare system, patient and private 3rd party payer, or some combination of these perspectives. This economic benefit would be even greater, if accounting for the persistent clinical improvement and preventive effect of AIT-outcomes that are not seen with SDT. One 6-year prospective study demonstrated 80% lower healthcare costs in the patients who received subcutaneous AIT (SCIT) compared with SDT, three years after the treatment discontinuation.

Several systematic review and meta-analysis of studies that evaluated the costs and benefits of SCIT and/or sublingual AIT (SLIT) and concluded that both forms of AIT may be cost-effective compared with SDT (Table 1). One analysis indicated AIT became cost-effective, as compared with SDT, after 6 years of treatment initiation from the patient and National Health Services (NHS) perspectives and 7 years from NHS perspective. In another analysis the cost-savings associated with AIT began

at 3 months and progressively increased through 18-month evaluation period. The reason(s) for this early treatment economic benefit can only be speculated but are likely multi-factorial and may include the benefits of an allergy specialist's care

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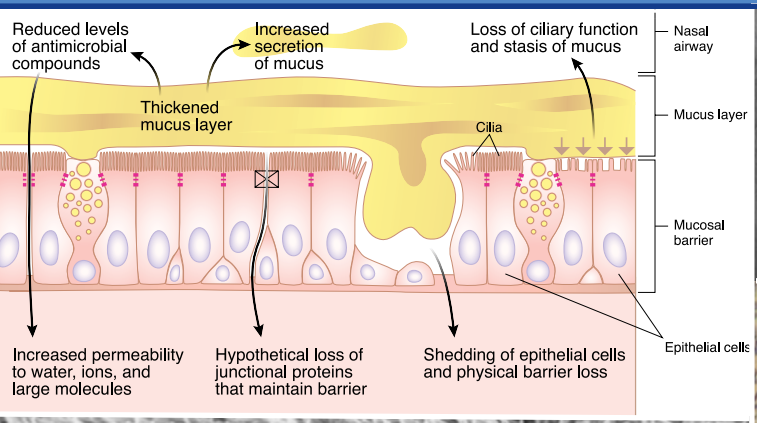
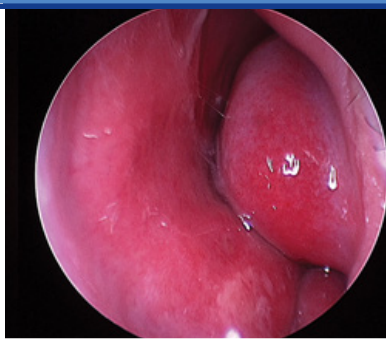
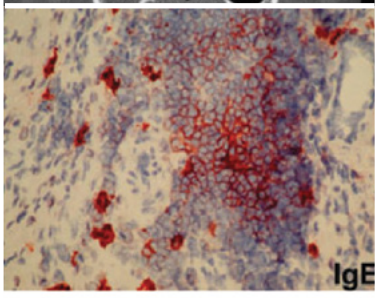
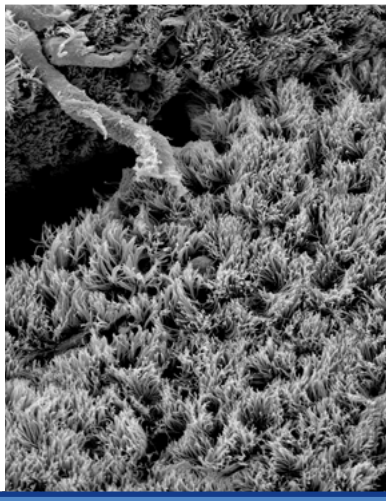
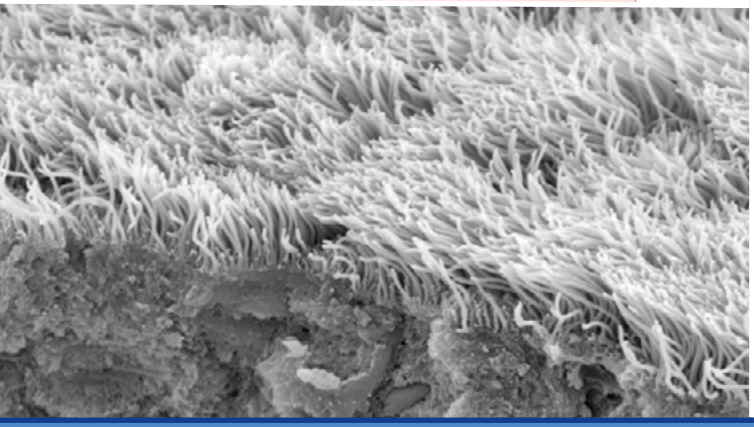
Section G

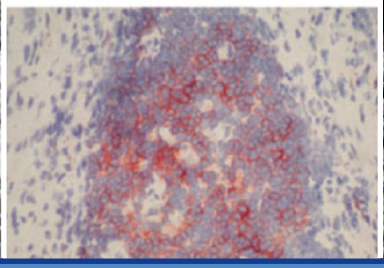












CHRONIC RHINOSINUSITIS (CRS) – MECHANISMS, EPIDEMIOLOGY, RISK FACTORS AND CO-MORBIDITIES

* Chronic rhinosinusitis - mechanisms
* Innate and acquired immunity and epithelial cell function in chronic rhinosinustitis
* The role of superantigens in allergic rhinitis, asthma and chronic rhinosinusitis
* Host-microbial interactions in chronic rhinosinusitis
* Immunodeficiency and chronic rhinosinusitis
* T-cell regulation in chronic paranasal sinus disease
* Cytokine profiles in chronic rhinosinusitis
* Mucociliary transport in chronic rhinosinusitis
* Airway remodeling in chronic rhinosinusitis
* Epidemiology of chronic rhinosinusitis
* Risk factors for chronic rhinosinusitis
* Classification of chronic rhinosinusitis
* Clinical features of chronic rhinosinusitis
* Endotypes and phenotypes of chronic rhinosinusitis
* Eosinophilic chronic rhinosinusitis
* Fungal sinus disease
* Co-morbidities of chronic rhinosinusitis
* Uncontrolled rhinosinusitis
* The global burden of chronic rhinosinusitis

1 CHRONIC RHINOSINUSITIS - MECHANISMS

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KEY MESSAGES

- Defects in the mucosal barrier and in the removal of allergens, microbes, mucus, and particulates from the air
- Frequent infections with bacteria, fungi, and viruses leading to clinical symptoms and either recurrent acute illnesses or chronic inflammation of the nose and sinuses
- Accumulation of immune cells including eosinophils, basophils, neutrophils, mast cells, T cells, and B cells that can produce mediators involved in immune cell recruitment, tissue injury, and perpetuation of the inflammatory response
- Growth of polyp tissue and/or widespread swelling and mucus production in the nose and sinuses

Chronic rhinosinusitis (CRS) is a complex disease associated with inflammation of nasal and sinus tissue. Currently, the cause of CRS remains unclear but researchers have proposed several mechanisms. In healthy people, the nose and sinuses are lined with epithelial cells and other specialized cells that form a mucosal barrier. This barrier serves to protect the underlying tissues from the millions of allergens, microbes, and particulates inhaled regularly. Such inhaled particles can be trapped in mucus and cleared through the action of cilia on nasal epithelial cells that move mucus out of the airways. In CRS, the mucosal barrier can be defective (Figure 1). Epithelial cells do not function normally, leading to a weak and permeable barrier. This impaired barrier is exposed to more particles and does not repair itself as well as a healthy barrier. There is increased thick mucus production in CRS that cannot be easily cleared away by nasal epithelial cilia.

Some people with CRS have persistent growth of fungi or bacteria such as *Staphylococcus aureus* in their nose and sinuses. In some cases, the organism does not cause significant damage to tissue. However, problems can occur if an immune response is mounted against the colonising organism or to the toxins it makes. This immune response can cause inflammation and damage to the sinus and nasal tissues and worsen CRS (Figure 2).

There are many types of white blood cells that play a role in CRS inflammation. Special factors released by epithelial cells and other cells can cause immune cells to migrate outside of blood vessels into the sinus and nasal tissue. Eosinophils, neutrophils, basophils, mast cells, innate lymphoid cells type-2, T cells, and B cells are elevated in CRS. These cells can be activated to release specific mediators that can recruit more immune cells, cause tissue injury, and perpetuate inflammation.

Inflammation in CRS can lead to the dilation of nasal and sinus blood vessels, tissue swelling, and increased mucus production (Figure 3). These features can produce common CRS symptoms including stuffy nose, runny nose, and sinus pressure. Finally, in certain types of CRS, nasal polyps can form which are not cancerous but are characterized by local swelling, fluid retention, and increased fibrin deposition.

In summary, many models have been proposed describing the

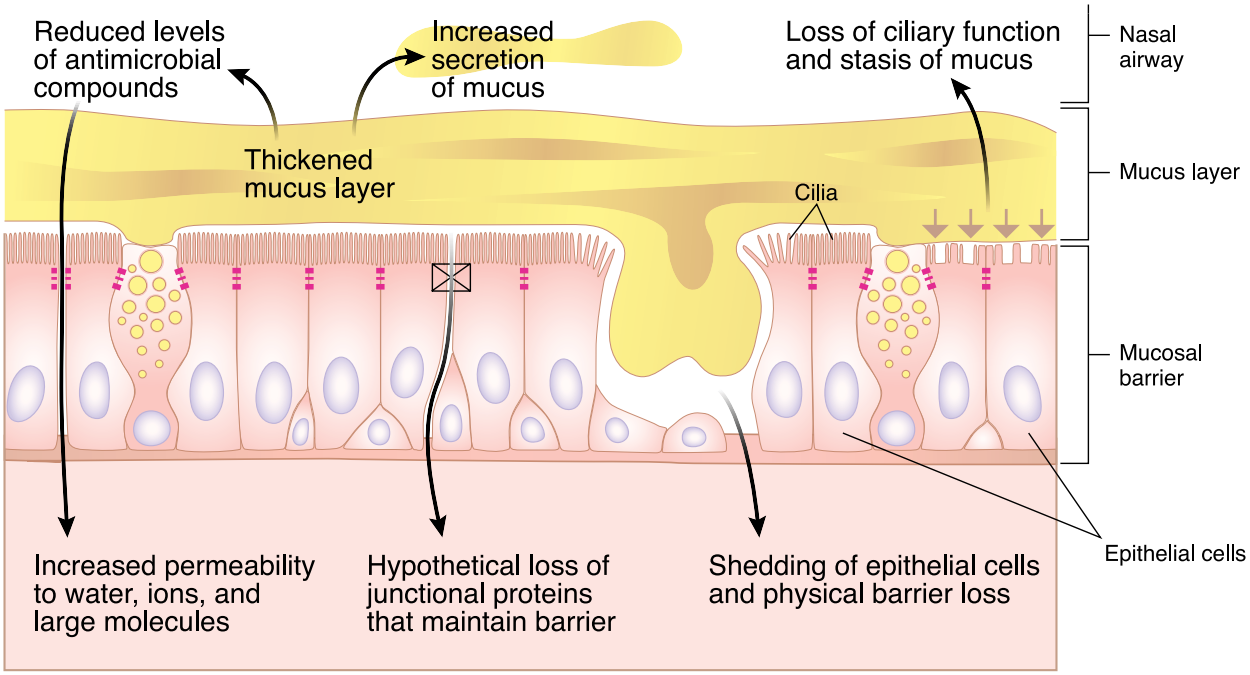

Figure 1 Components of the mucosal barrier in CRS may be defective.

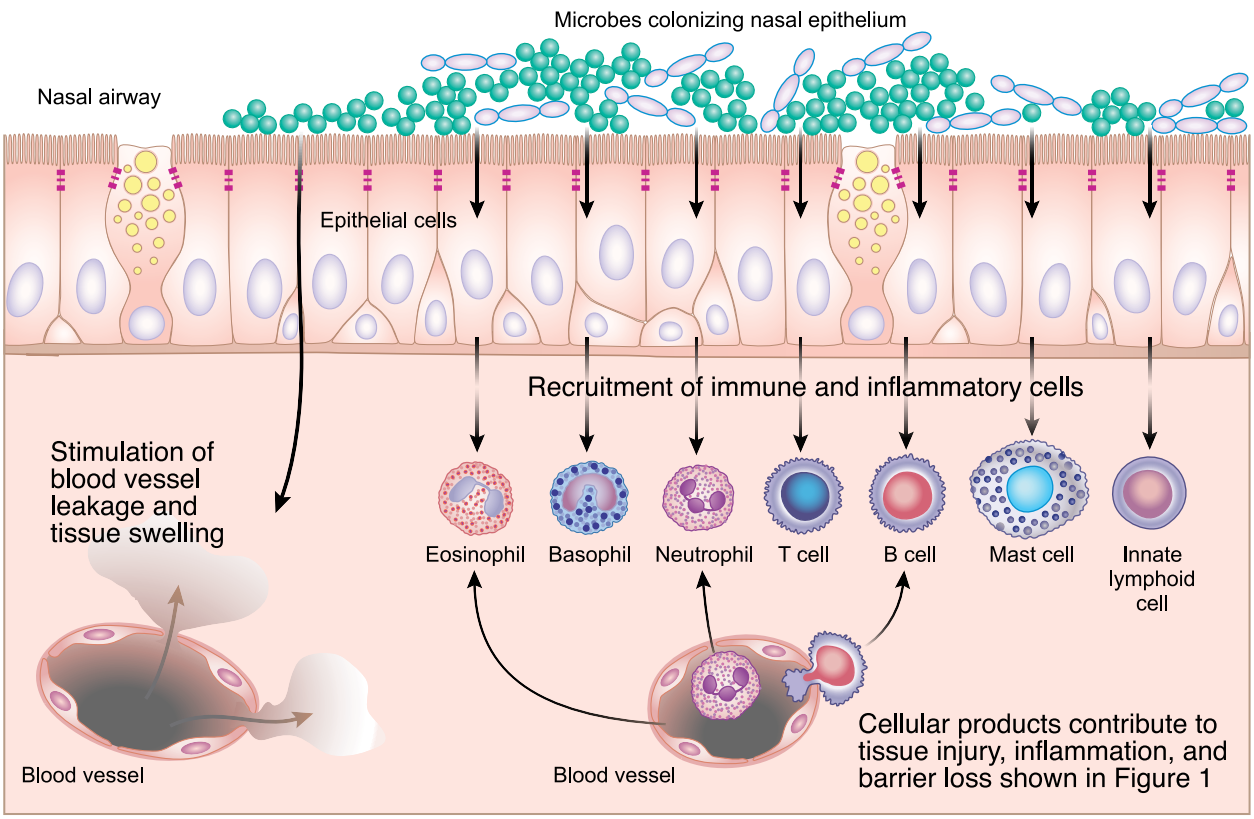

Figure 2 Colonization with microbes and accumulation of immune cells can lead to tissue injury, inflammation, and mucosal barrier loss in CRS.

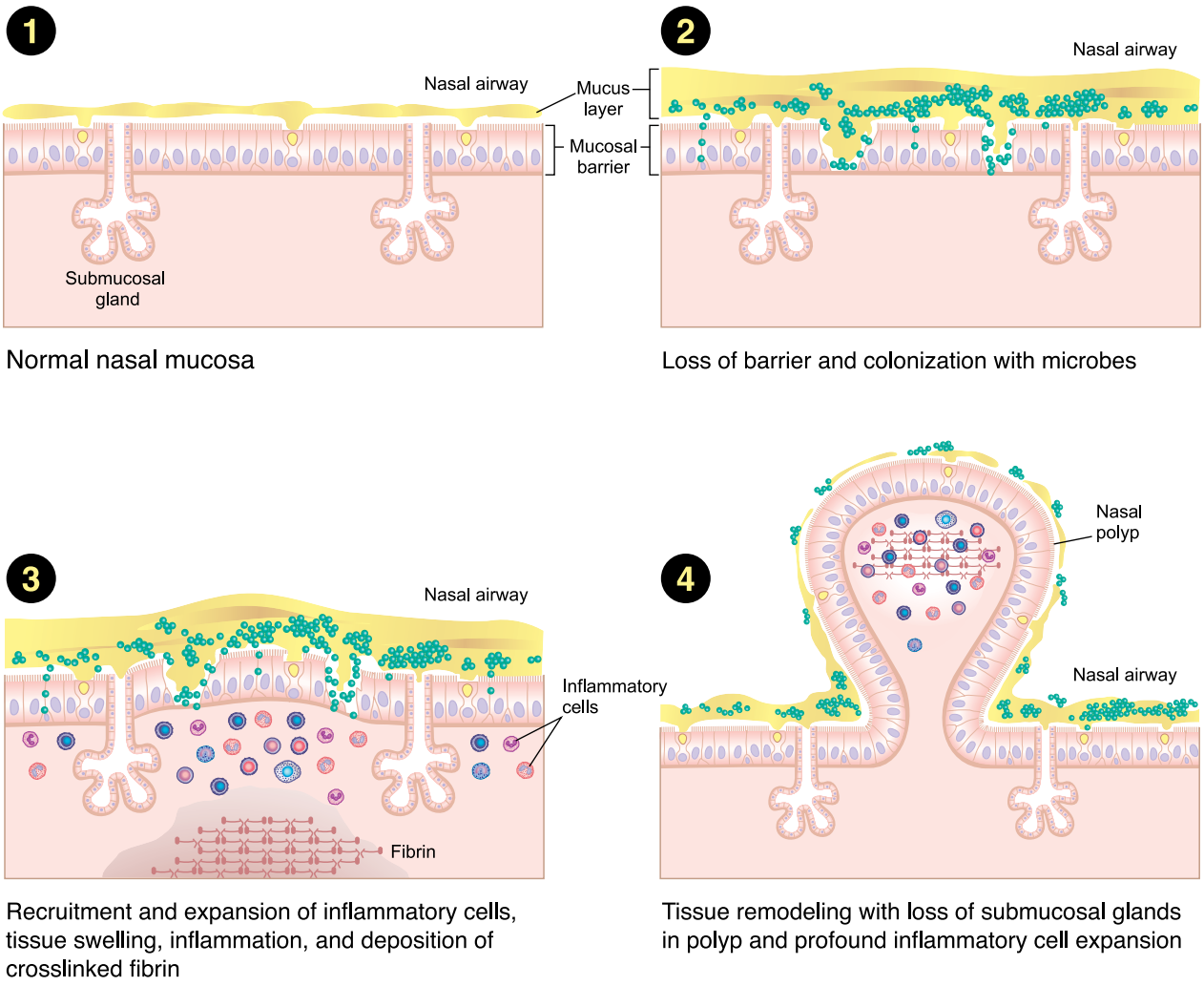

Figure 3 Formation of nasal polyps involves tissue remodeling and enhanced inflammation.

mechanisms of CRS. It is very likely that mucosal barrier integrity, pathogen colonization, and the ensuing immune response all play important roles.

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2 INNATE AND ACQUIRED IMMUNITY AND EPITHELIAL CELL FUNCTION IN CHRONIC RHINOSINUSTITIS

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KEY MESSAGES

- The innate immune system represents the first line of immunity and host defense and can influence the specific acquired, adaptive immune response or the epithelial surface
- The innate immune system distinguishes microbes and other entities on a molecular basis. These molecular patterns that are recognized impinge on a variety of receptors
- The mechanisms of innate immunity in maintenance of the upper airway epithelium requires cellular functions that range from epithelium itself through a variety of resident immune cells and infiltrating inflammatory cells
- The T-lymphocytes may develop a specific type 2 adaptive immune response. The triggering of these specific cells by allergens, viral, and microbial proteins may trigger the symptoms of rhinosinustitis

Microbial pattern recognition is a major function of the innate immune system mediated by a variety of cells in the tissues predominately at the epithelial airway interface in the nose and sinuses. There are four types of receptor mechanisms activated in this kind of pattern recognition response (Table 1). The first involves membrane bound receptors, such as the Toll like receptors (TLR) and C-type lectin receptors, all of which are involved in immune cell activation, cytokine production and regulation and other mediator release. The second level response involves secreted membrane browned form of receptors from microbial proteins and other agents. These would include CD14 that binds endotoxin as does LPS-binding protein, and all of these secreted membrane browned material are potentially co-factors for TLR activation. The secreted forms of host defense in innate immunity involves the production of anti-microbial peptides including the defensins, celliicidin, dermicidin and the collectins, surfactant proteins and C-reactive protein. Finally cytosolic receptors that are NOD-like of which the genes coding for NOD1 and 2, and NLRP 1, 3 and 4. All pattern recognition receptors play a role in the generation of an intact inflammasone that could be generated in response to innate immune response system activation. Once these innate processes are activated, a variety of signaling pathways generated by the various receptors, membrane and cytosolic lead to a development of pro-inflammatory cytokines and other proteins that are involved not only in direct host defense, but also in the initiation and modulation of adaptive immunity, either locally within the submucosa, or within the draining lymphoid tissues (Figure 1).

These immune responses depend on a wide variety of factors ranging from the microbiome identified in the upper airway dependent on exposure and development of microbiological systems on other surfaces including the skin and gut. In the airways, these bacterial enviropathogens and/or commensals do significant influence the type of immune response generated. Most functional immune responses that are adaptive derive from innate immune responses are Th1 and Th17 dependent responses, In those individuals, who have a genetic predisposition for

TABLE 1

Pattern Recognition Receptors	
Membrane bound	Toll like receptors, C-type lectin receptors
Membrane bound and sealed	CD14, LPS binding protein
Secreted	Antimicrobial peptides: defensins, celliicidin, dermicidin and the collectins, surfactant proteins and C-reactive protein
Cytosolic	NOD1, NOD2, NLRP1, NLRP3

LPS = lipopolysaccharide; NOD= nucleotide-binding oligomerization domain; NLRP = NOD-like receptors

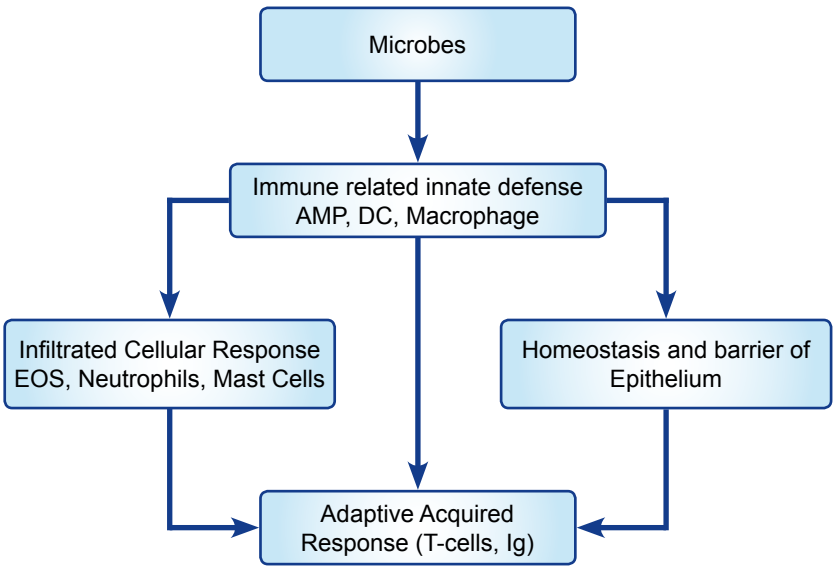

Figure 1 Innate Defense modulates the adaptive immune response. AMP = antimicrobial peptide; DC = dendritic cell, EOS = eosinophils; Ig = immunoglobulins.

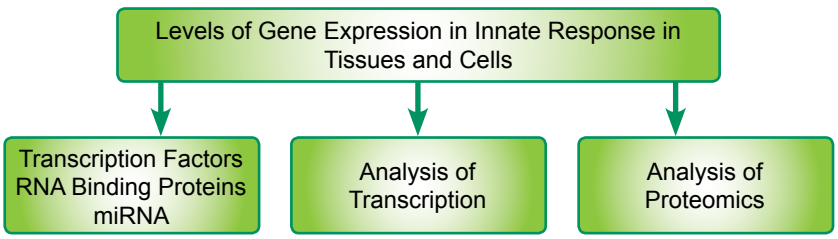

Figure 2 Investigation of the innate immune response by multiple omics.

type 2 immune responses, Th2 responses can be developed and can influence the landscape of the epithelium. In the presence of increased IL4 and IL13, there is reduced production of antimicrobial peptides and defensins, as well altered barrier function of the epithelium.

Finally, it is entirely possible that the mechanisms of immune responses in chronic rhinosinusitis (CRS) could give a hint as to the organization and systems biology of innate immunity at the epithelium border (Figure 2). So, there is an inference for excess mRNA production in response to an innate and/or an adaptive trigger in which gene activation leads to increased mRNA. This increased mRNA activity can be correlated with excess protein of pro inflammatory nature that would be generated. Transcription factors, RNA binding proteins, and miRNA's influence the mRNA output in terms of gene output, so those are important regulatory factors.

The innate immune system can be evaluated in a variety of pathway analysis that would identify potential pathway commons and/or unique aspects of innate adaptive immune interactions based on network evaluation of high throughput data such as after allergen exposure, during allergen immunotherapy, or under influenza immunization and/or exposure to natural viruses. All of these activities across the respiratory upper airway epithelium can be assessed and measured. An identification of new potential mechanisms for innate adaptive immune responses in CRS will be most interesting and identify important models that can be developed for understanding the framework of allergic disease mechanisms.

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3 THE ROLE OF SUPERANTIGENS IN ALLERGIC RHINITIS, ASTHMA AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Superantigens, best known those from *Staphylococcus aureus*, can stimulate the mucosal immune system and aggravate disease
- *S. aureus* frequently colonizes noses in children and is associated with an increased risk for asthma
- Allergic rhinitis and asthma patients frequently develop IgE against superantigens (SE-IgE)
- In chronic rhinosinusitis with nasal polyps, SE-IgE can be found in the tissue and are associated with severe disease and comorbid asthma
- Serum SE- IgE is associated with asthma, and specifically with severe asthma, hospitalisations and decreased lung function
- Omalizumab reduces polyps and symptoms also in non-atopic SE-IgE positive subjects

Staphylococcus aureus superantigens were recognized by their unique property to stimulate T-cells via the T-cell receptor unrestricted by its antigen specificity, and have been shown to broadly activate epithelial cells, dendritic cells, B-lymphocytes as well as mast cells and eosinophils. Although this interaction is not restricted to a mucosal Th2 bias, there is an association between *S. aureus* colonisation, formation of IgE antibodies to superantigens (SE-IgE) and allergic airway disease (Figures 1 and 2). There is evidence that allergic mucosal sites show a deficit in defense against *S. aureus* partially due to the alternative activation of macrophages (type 2 macrophages) in the upper and lower airways. Nasal colonisation with *S. aureus* is associated with increased risk of asthma prevalence, symptoms, and exacerbations in children and young adults. It has been recently speculated that the epidemic of *S. aureus* colonisation may drive the concurrent epidemic of asthma.

As superantigens also stimulate B-cells and induce receptor revision and class switch recombination, an increased and often polyclonal IgE formation is typically found in the mucosal site, producing high concentrations of functional IgE antibodies. In subjects with allergic rhinitis (AR), with or without allergic asthma, a significant increase in the prevalence and concentration of IgE antibodies to classical superantigens vs. controls was found, likely contributing to more severe symptoms. Europe-wide, the finding of SE-IgE antibodies in serum is associated with higher total IgE concentrations and an increased risk of asthma (OR 2.10 [1.60–2.76], P = 0.001) in a concentration-dependent manner in atopic and non-atopic subjects. In asthmatics, serum SE-IgE is associated with asthma severity, oral corticosteroid use, hospital admissions and decrease in lung function.

Apart from AR and asthma, *S. aureus* and SE-IgE does also play a prominent role in chronic rhinosinusitis (CRS), especially in the nasal polyp (NP) phenotype. In Europe, 85% of NP are Th2-biased and eosinophilic, with a low to medium expression of interleukin-5 and IgE. *S. aureus* has been demonstrated to reside intramucosally, and to release superantigens locally, orchestrating

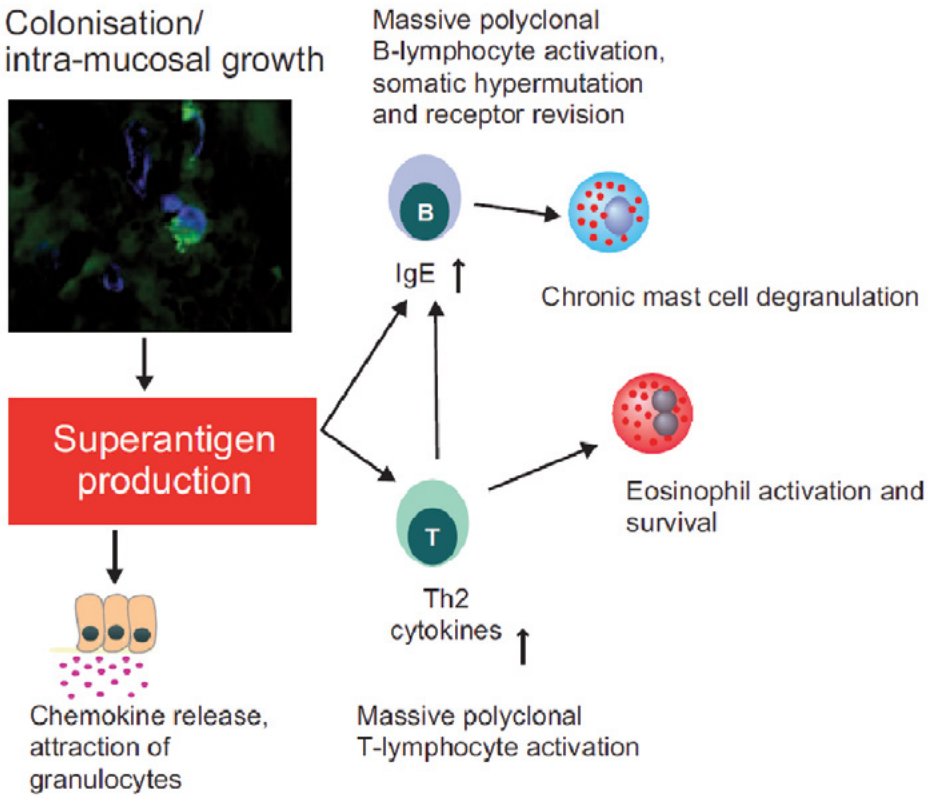

Figure 1 Mucosal effects of *S. aureus* superantigens on immune cells.

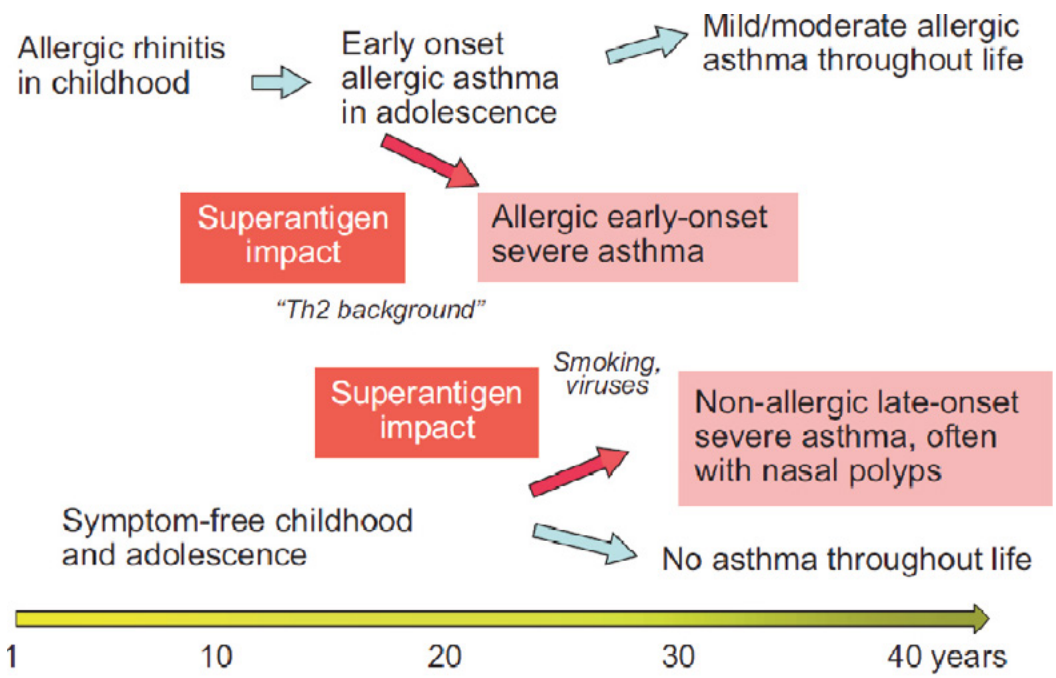

Figure 2 Impact of *S. aureus* and its superantigens on airway disease throughout lifetime.

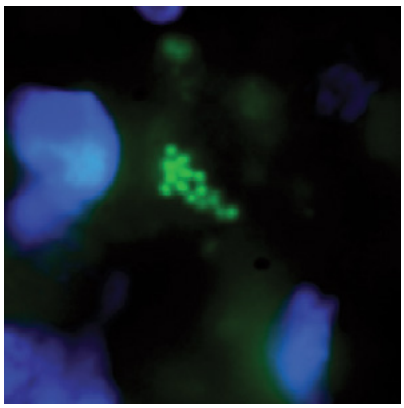

Figure 3 Intramucosal *S. aureus* in a polyp sample.

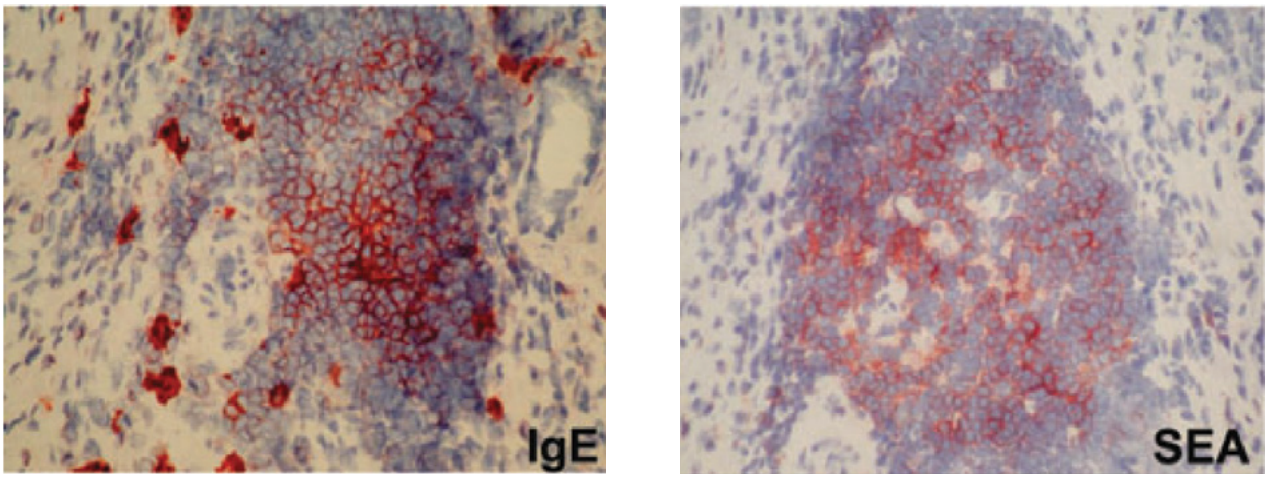

Figure 4 Follicle-like structures in a nasal polyp expressing IgE and binding the superantigen SEA.

a severe eosinophilic inflammatory reaction with high total IgE concentrations (Figures 3 and 4). Tissue SE-IgE, which is found in up to 25% of NP patients, significantly increases the odds ratio to have comorbid asthma, and also is a predictor for NP recurrence after surgery. Of interest, Omalizumab has been demonstrated to significantly reduce NP size and decrease symptoms in patients with NP and asthma, independent of the atopic status. These patients suffer from late-onset non-atopic disease, which is likely to be orchestrated by staphylococcal superantigens.

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4 HOST-MICROBIAL INTERACTIONS IN CHRONIC RHINOSINUSITIS

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Chronic rhinosinusitis (CRS), exists in 3 subtypes, namely CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP) and allergic fungal rhinosinusitis (AFRS). Host-microbial interactions (HMI) are key to the pathogenesis of CRS manifesting as an unusual susceptibility to infection, biofilm formation, "dysbiosis" of the nasal/sinus microbiome or "maladaptive" Th2-biased immune responses to microbial colonization. Defects in host innate immune responses potentiate these phenomena.

Bacterial biofilm forms on sinus mucosa with an overall prevalence of 56.3% in surgical CRS series but less in CRSwNP. The presence of polymicrobial biofilm or biofilm containing *Staphylococcus aureus* has been associated with more severe sinus disease preoperatively and worse sinus symptom and nasal endoscopy scores postoperatively. An intraepithelial reservoir of *Staphylococcus aureus* (IESA) has been demonstrated in CRS patients, but its significance is unclear. The key features of "dysbiosis" of the sinus microbiome are summarized in Table 1. While the total bacterial burden in CRS tissue is similar to controls, there is an increased "burden" of *Staphylococcus aureus*. Certain bacterial taxa or species may be protective against CRS, whereas others may be uniquely harmful, although these observations derive from only one study. There is debate regarding the importance of colonizing fungi as drivers of maladaptive Th2 inflammation in CRS, stemming in part from difficulties in staining fungal hyphae or culturing viable fungi from sinus mucus samples

KEY MESSAGES

- Host-microbial interactions (HMI) are key to the pathogenesis of chronic rhinosinusitis (CRS) manifesting as: infection with or without biofilm formation, "dysbiosis" of the nasal/sinus microbiome or maladaptive immune responses to microbial colonization
- Multiple host functions protect against sinus infection and maintain a healthy sinus microbiome, including epithelial barrier, mucociliary clearance, microbial recognition through innate epithelial pattern-recognition receptors and production of antimicrobial proteins and nitric oxide (NO)
- A deficiency in local production of lactoferrin has been described in CRS
- A nonfunctioning polymorphism in the bitter taste receptor T2R38 fails to recognize a quorum-sensing molecule from *Pseudomonas aeruginosa*. CRS patients possessing this nonfunctioning polymorphism (TAS2R38) are more likely to have *Pseudomonas* sinus infection
- *Staphylococcus aureus* can contribute to CRS pathogenesis by several mechanisms: overt infection, mucosal biofilm, intraepithelial colonisation and by staphylococcal enterotoxins (SEA, SEB or TSST-1) that activate T lymphocytes to produce Th2 cytokines (IL-5 and IL-13) and elicit local maladaptive anti-enterotoxin IgE antibodies in nasal polyps
- Certain colonising fungi also elicit maladaptive Th2 responses in CRS

TABLE 1

Key findings regarding "dysbiosis" of the microbiome in CRS patients
• Less richness, evenness and diversity in CRS than controls.
• Total bacterial burden in CRS is similar to controls.
• Increased burden for certain organisms (e.g. *Staphylococcus aureus*).
• Certain bacterial taxa or species may be protective (e.g. the order *Lactobacillales* or the species *Lactobacillus sakei*), although this has not been supported in all studies.
• Some taxa or species may be uniquely harmful (e.g. the family Corynebacteriaceae and the species *Corynebacterium tuberculostearicum*), although this has not been supported in all studies.

and in part from conflicting results regarding the immune stimulation afforded by colonizing fungi.

Table 2 summarizes the key components involved in host-microbial interactions in the paranasal sinuses. Tight junction proteins, adherens junction proteins and desmosomal proteins maintain normal epithelial barrier function. No primary defects in these proteins have been described in CRS or NP, although decreased occludin and zonula occludens 1 and decreased E-cadherin were described in NP, likely secondary to allergic tissue inflammation. CRS is associated with a transient reduction in mucociliary clearance that normalizes following resolution of infection and restoration of sinus ostial patency. There is no evidence for a primary defect in mucociliary clearance in CRS except in the rare patients with primary ciliary dyskinesia (PCD) and cystic fibrosis (CF). A decreased level of the antimicrobial protein lactoferrin has been found in CRS, whereas the level of other antimicrobial proteins has been found to be normal. Nitric oxide (NO) is constitutively produced at high levels in sinus epithelium by virtue of constitutive expression of inducible nitric oxide synthase (iNOS). The NO concentration in a healthy maxillary sinus (9.1 +/- 3.8 ppm) exceeds that necessary for antibacterial effects *in vitro* and is vastly higher than that produced in the nose or lungs (exhaled NO normally < 50 ppb).

Figure 2 summarizes current knowledge about microbial triggering of innate immune responses in CRS. Sino-nasal epithelial cells express Toll-like receptors (TRLs) that recognize pathogen-associated molecular patterns (PAMPs) leading to production of antimicrobial peptides and cytokines and chemokines that amplify innate and adaptive immune responses. No primary defects in sino-nasal TLRs have been described in CRS. Dectin and NOD-like receptors have not been studied in CRS. Bitter taste receptors, such as TAS2R, recognize besides bitter taste a quorum-sensing molecule from *Pseudomonas aeruginosa* resulting in production of antimicrobial NO and β-defensin. A common polymorphism (TAS2R38 variant) is associated with reduced signaling and an increased frequency of *P aeruginosa* infection in CRS patients.

There is evidence that links colonizing microorganisms to a maladaptive Th2-biased "local allergic" response in NP. Certain fungi, such as *Alternaria*, induce production of IL-5 and IL-13, as well as IFN-γ in peripheral blood lymphocytes from CRS patients and elicit modest production of IL-5 and IL-13 from dispersed NP T lymphocytes. Mucosal colonization with *Staphylococcus aureus* occurs in 64% of patients with CRSwNP, compared with 30% in healthy individuals or patients with CRSsNP, and staphylococcal superantigens (such as SEB) cause local proliferation of T lymphocytes, local anti-SEB IgE antibody production and robust production of IL-5 and IL-13 in dispersed NP T lymphocytes. These studies suggest that colonizing *Staphylococcus aureus* is a major driver of the local maladaptive Th2-biased inflammatory response in CRSwNP. There is also evidence that links allergic inflammation with down-regulation of TLR-9 expression which may account for some of the increased susceptibility of NP toward bacterial colonization.

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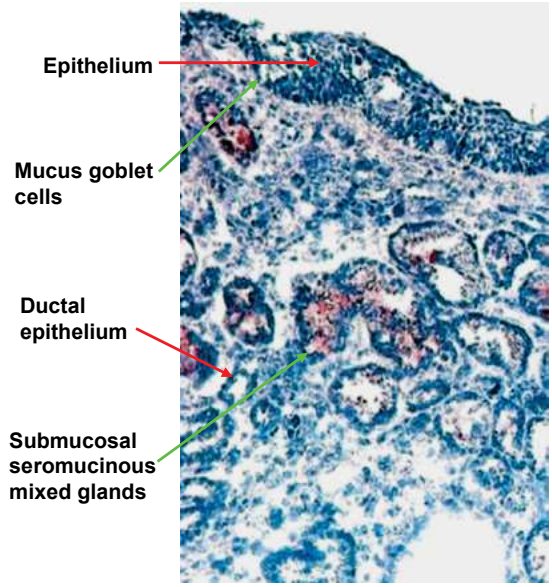

Antimicrobial proteins/antimicrobial peptides: Lactoferrin, lysozyme, S100A7 (psoriasin) and S100A8/A9 (calprotectin), LPLUNC-1, short-PLUNC1, LPLUNC-2 (BPI), α-defensin, β-defensins (HBD-1, HBD-2) and cathelicidin (LL-37).

Immunoglobulin-related proteins: Secretory IgA, secretory component (extracellular component of poly-Ig receptor), BAFF (B cell-activating factor)

Complement-related proteins: C3, Factor B, Factor H, serum amyloid A

Chitinases: Acidic mammalian chitinase (AmCase), chitotriosidase

Ficolins and collectins: SP-A, SP-D, uteroglobin (secretoglobin), statherin, mammaglobin B

Secretory proteins: Lipocalin-1, neutrophil gelatinase-associated lipocalin (NGAL)*

Phospholipases/Proteases/Protease inhibitors: Secretory phospholipase: sPLA(2)-IIA, -IID, -IIE; MASP1, MASP2, secretory leukocyte protease inhibitor (SLPI)

Antimicrobial reactive species: nitric oxide (NO)

Figure 1 Structure of sinus epithelium, submucosal seromucinous mixed glands and stroma and summary of the most widely studied proteins and peptides and antimicrobial substances produced by sinus mucosal cells of relevance to CRS. Seromucinous glands are stained positively for CXCL1 (GRO-α). (*Adapted from Hamilos DL. Host-microbial interactions in patients with chronic rhinosinusitis. J Allergy Clin Immunol 2014;133:640-653.*)

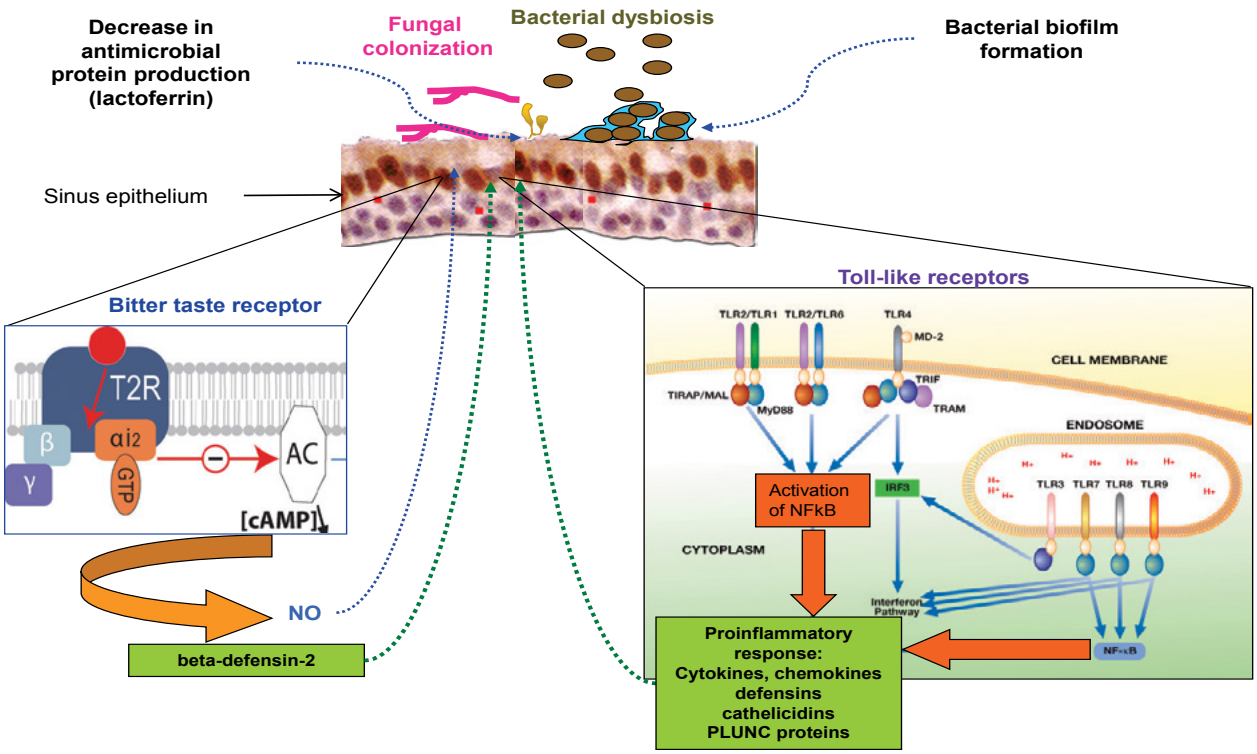

Figure 2 Summary of pathologic features of CRS and important components of innate immunity of relevance to CRS. (Not all pathologic features need be present in all cases.). (*Adapted from Hamilos DL. Host-microbial interactions in patients with chronic rhinosinusitis. J Allergy Clin Immunol 2014;133:640-653.*)

TABLE 2

Key components involved in host-microbial interactions in the paranasal*

Host function	Key innate components or receptors in airway epithelial cells	Specific receptors or proteins involved	Relevant pathogens	Defects in CRS patients
Maintaining epithelial barrier	Tight junction proteins	claudins, occludins	Bacteria, fungi	Decreased in NP epithelial cell cultures.
	Adherens junction proteins	E cadherin		Decreased in NP.
	Desmosomal proteins	desmoglein 2 desmoglein 3		Decreased in NP epithelial cells in response to IL-13.
Mucociliary clearance	Cilia	Outer dynein arms, inner dynein arms, or both	Gram-positive and gram-negative bacteria	CRS patients with PCD.
Mucus rheology	Epithelial chloride channels	CFTR	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*	CRS patients with CF.
Innate epithelial pattern-recognition (cell membrane or intracellular TLR)	TLR 1-10 that recognize specific bacterial cell wall component, viral double-stranded RNA (dsRNA), and bacterial unmethylated CpG ODN sequences (CpG DNA) [1,2]	TLR2	Gram-positive and Gram-negative bacteria; fungi	Normal function in CRS.
		TLR3	Rhinovirus, other viruses	Normal function in CRS.
		TLR4 (recognizing LPS)[3]	Gram-negative bacteria; *Candida* and *Aspergillus fumigatus*	Normal function in CRS.
		TLR9	Bacteria	Reduced TLR9 in cultured NP epithelial cells possibly due to Th2 cytokines.
Bitter taste receptors (e.g. T2R38, TAS2R)	G-protein coupled receptors expressed on sinus epithelial cells that recognize bitter tastes and quorum-sensing molecules.	TAS2R38	*Pseudomonas aeruginosa*	Nonfunctional TAS2R38 genotype correlated with *P aeruginosa* infection in CRS patients
Antimicrobial proteins	Produced in response to TLR ligation and to bitter taste receptor ligation	Lactoferrin, lysozyme	Bacteria, fungi	Decreased lactoferrin in CRS
		Beta-defensins	Bacteria	Normal levels in CRS.
		Cathelicidins	Bacteria	Normal levels in CRS.
		Bactericidal/permeability increasing protein (BPI)	Gram-negative bacteria	Decreased in NP (likely reflecting less glands in NP).
		Complement C3, serum amyloid A	Bacteria, fungi	Normal levels in CRS.
		Psoriasin, calprotectin	Bacteria, fungi	Decreased in NP

[1] *TLR-1, -5, -6 and -10 are not included, because there are no reports of abnormalities in these TLRs associated with CRS.*

[2] *CpG: bacterial deoxyribonucleic acid (DNA) containing unmethylated CpG dinulceotides.*

[3] *LPS; lipopolysaccharide.*

TLR ligand information sources: http://www.invivogen.com/tlr2-ligands

** Data from Hamilos DL. Host-microbial interactions in patients with chronic rhinosinusitis. J Allergy Clin Immunol 2014;133: 640-653.*

5 IMMUNODEFICIENCY AND CHRONIC RHINOSINUSITIS

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Chronic rhinosinusitis (CRS) is associated with significant morbidity and a high healthcare burden. Risk factors associated with CRS include atopy, structural abnormalities and immune dysfunction. Thus, patients with CRS who are refractory to medical therapy, or those who present with recurrent sinus infections, are evaluated for immunodeficiency.

Antibody deficiencies, such as specific antibody deficiency (SAD), common variable immunodeficiency (CVID), and selective IgA deficiency are among the primary immunodeficiencies (PID) that are associated with CRS (Tables 1,2). Antibody deficiencies should be considered in patients with CRS refractory to standard medical and surgical management.

KEY MESSAGES

- Antibody deficiencies are the most common primary immunodeficiencies. Patients with antibody deficiencies are susceptible to bacterial pathogens and can develop recurrent or chronic upper and lower respiratory tract infections. It is important to recognize antibody deficiencies in patients with refractory rhinosinusitis
- Common variable immunodeficiency, selective IgA deficiency, and specific antibody deficiency account for the majority of antibody deficiencies observed in patients with chronic rhinosinusitis (CRS)
- Antibody deficiencies range in severity from mild to severe depending on the underlying pathology and levels of antibody production and function
- Treatment options of antibody deficiencies in patients with refractory CRS should be individualized and may include prophylactic antibiotics and immunoglobulin replacement

COMMON VARIABLE IMMUNODEFICIENCY

Common variable Immunodeficiency (CVID) is the most common symptomatic antibody deficiency. Typically there is a reduction in at least two of the three major immunoglobulin types: levels of IgG as well as IgA and/or IgM are reduced more than two standard deviations below the mean adjusted for age. In addition, there is an impaired antibody response to immunization with polysaccharide antigens and often to protein antigens. Quite often CVID is diagnosed in the second and third decade of life although symptoms may precede the diagnosis by many years. Recurrent infections involving the upper and lower respiratory tracts are often observed in CVID. The prevalence of CVID in patients with CRS at academic institutions ranges from 6-10%. In a European cohort study, CRS was present in 37% of CVID patients at diagnosis and increased to 54% after 11 years of follow up. CVID is a heterogeneous disorder with both infectious and noninfec-

TABLE 1

Prevalence of common primary antibody immunodeficiencies in patients with chronic rhinosinusitis who were evaluated for Immunodeficiency at an academic institution

Immune Status	Patients
Specific Antibody Deficiency (SAD)	144 (24.2%)
Common Variable Immune Deficiency (CVID)	35 (5.9%)
IgA deficiency	16 (2.7%)
No Immunodeficiency	402 (67.6%)
Total	**597**

TABLE 2

Phenotype and clinical features of common primary antibody deficiencies observed in patients with chronic rhinosinusitis

Subtype	Clinical Features	Immunological Features
Pan-hypogammaglobulinemia (CVID)	Upper and lower respiratory tracts bacterial infections, autoimmune diseases, increased risk of malignancy	1. Decreased CD27+ memory B cells 2. Defective plasma cells 3. Decreased immunoglobulins
Selective IgA deficiency	Typically asymptomatic, may get recurrent bacterial respiratory tract infections	1. Pathogenesis not known 2. IgA < 0.07g/L, normal IgG and IgM
Specific antibody deficiency	Bacterial infections; most are asymptomatic	1. Normal immunoglobulins 2. Lack of functional response to polysaccharide vaccines

CVID, common variable immunodeficiency

tious comorbidities. Many patients with CVID have noninfectious complications including chronic lung disease, autoimmunity, lymphoma, granulomatous disease or inflammatory gastrointestinal disease. In addition, patients with CVID have a reduced lifespan when compared to the general population. These findings highlight the importance of diagnosing CVID in at-risk patients, including those with recurrent sinus infections or refractory CRS.

SELECTIVE IgA DEFICIENCY

Prevalence of **selective IgA deficiency** ranges from 1 in 173 to 1 in 3024 persons. The prevalence may be increased in CRS and was reported in 3-6% of patients with CRS, who were evaluated for immunodeficiency. The majority of patients with IgA deficiency are asymptomatic, however a small subset develops recurrent sinus infections or CRS. Atopy, asthma, and autoimmune diseases are also common in patients with IgA deficiency.

Patients with **specific antibody deficiency** (SAD) form normal quantities of IgG antibodies, but the antibodies don't function well. SAD is diagnosed by demonstrating a poor response after a polysaccharide vaccine: typically 50-70% of pneumococcal serotypes should be at or above a protective level (>1.3 mcg/mL) after an unconjugated pneumococcal polysaccharide vaccine. In an academic setting, up to 24% of patients with CRS, who were evaluated for immune problems had SAD. These patients received more antibiotic courses compared to patients with CRS who had an intact immune system, had an increased incidence of pneumonia, and 18% of the patients with SAD were treated with immunoglobulins.

IgG SUBCLASS DEFICIENCY

IgG subclass deficiency is defined as one or more low IgG subclasses with normal total IgG levels. The clinical significance of an isolated IgG subclass deficiency is controversial. Low levels of IgG subclasses have been reported in otherwise healthy individuals. It is believed that a lack of a functional response to a polysaccharide vaccine is more important than deficiency in IgG subclasses. For this reason, routine determination of IgG subclasses is not recommended in the evaluation of immunodeficiency in patients with CRS.

THERAPY

Treatment options for patients with CRS and antibody deficiency should be individualized and may include the use of prophylactic antibiotics as well as vaccination with a conjugated pneumococcal antigen vaccine. Immunoglobulin replacement is reserved for patients with CVID or those who fail to respond to vaccinations and have persistent infections. The underlying CRS should be managed by medical therapy and if necessary by surgical intervention.

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6 T-CELL REGULATION IN CHRONIC PARANASAL SINUS DISEASE

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KEY MESSAGES

- The role of the specific immune system in the upper airways is particularly interesting as the large surface in combination with the innate immune components and the mucosal surface represents a first contact point of immune system and inhaled environment including certain antigens
- Upon allergen-airway challenge T cells start to express enzymes encoded by the recombination-activating genes that edit the germline genes of the B- and T cell receptors and also the switch of naïve, IgM+ B cells to IgE
- The analysis of T cells isolated from chronically affected patients show a diverse cytokine secreting phenotype that is thought to origin from a "plasticity" of T cells
- A possible explanation for the origin of this cytokine escalation is the constant and repetitive exposure of upper airway cells to bacterial superantigens
- Increased cytokine production by the T cells is followed by an extended mediator release of tissue cells

While the structure of the upper airways gives rise to all kind of speculations regarding the evolutionary origin, it's function as interface to the environment is not in question. The role of the specific immune system is particularly interesting as the large surface in combination with the innate immune components and the mucosal surface represents a first contact point of immune system and inhaled environment including certain antigens.

IMMUNE SYSTEM OF THE UPPER AIRWAYS

A key hypothesis in T cell biology is that the antigen is taken up by dendritic cells and /or drained into the next lymph node, where antigens are presented in context with MHC class II to T cells and mobilize either de novo or memory responses along with help to differentiating B cells. In contrast to the lower airways the existence of the nasal mucosa associated lymphoid tissue (MALT) is less clear and therefore the turnover of lymphocytes is not fully known. However, it could be demonstrated that upon allergen-airway challenge T cells start to express enzymes encoded by the recombination-activating genes. These enzymes are expressed to edit the germline genes of the B- and T cell receptors and also the switch of naïve, IgM+ B cells to IgE. These studies demonstrate that lymphoid tissues are not essential for the maturation of the immune system and raise the question to which degree the tissue environment contribute to the maturation of the immune cells.

T CELL SUBSETS

While it is well established that T cells play a key role in the switch of uncommitted, IgM^+ B cells into IgG^+ or IgA^+ or IgE^+ memory phenotypes, it became apparent that T cells do also play a key role in the instruction of tissue cells such as epithelial cells. In fact IL-17 and IL-22 represent two T cell cytokines which act primarily or even exclusively on epithelial cells or keratinocytes. This finding raised the hope that paranasal sinus diseases could be treated with biologicals to block these cytokines. However, the analysis of T cells isolated

from local inflammation opposed to those that have been classically isolated from peripheral blood displayed a phenotype that differs from classical Th1, Th2, Th17 or Treg cells. While the classical T cell phenotypes express a narrow bandwidth of cytokines, the cells isolated from chronically affected patients show a more diverse phenotype that is thought to origin from a "plasticity" of T cells. This plasticity has been reported for Th1 cells from peripheral blood that are able to express IL-17 or IL-4 or Th2 cells expressing IFN-g, however expression can be reversible at least upon *in vitro* culture. Analysis of T cells from biopsies of patients suffering from chronic disease revealed that these T cells expressing multiple cytokines are not the exception, but rather a rule. In contrast to peripheral blood cells, these clones are remarkably stable, These cells do not show a particular polarization towards any of the effector phenotypes, but a depression of regulatory phenotypes.

ORIGIN OF THE CYTOKINE ESCALATION

A possible explanation for the origin of this cytokine escalation is the constant and repetitive exposure of upper airway cells to *Staphylococcal aureus* and its superantigens, which can activate the T cell receptor by cross-linking it with the MHC class II molecule, even in the absence of an antigen, which is normally located in the MHC-grove. This superantigen function may stepwise extend the T cell repertoire to produce cytokines.

REBOUND OF THE TISSUE

The multitude of cytokines has functional consequences not only on other immune cells, but also on structural cells such as airway epithelial cells. At least from the pharmaceutical viewpoint most monovalent drugs targeting cytokines were unsuccessful, while biologicals with broader specificity that are hitting multiple targets appear to be more effective. In fact, it appears that structural cells require the exposition to multiple cytokines before becoming themselves active in the expression of defence mechanisms. Consequently, increased cytokine production by the T cells will also be followed by an extended mediator release of tissue cells. Taken together, it appears that future therapies may need to address immune cells and tissue cells at the same time to revert excessive immune activation and insufficient regulatory control.

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7 CYTOKINE PROFILES IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Cytokines profiles differ among different phenotypes of chronic rhinosinusitis (CRS)
- Different cytokine profiles may underline different CRS endotypes
- The pattern of inflammation differs considerably between CRS with nasal polyps (NP), CRS without NP and CRS with NP accompanying cystic fibrosis
- Characterization of cytokine-producing cells and the whole array of cytokines in this context is demanded to generate more precise therapeutic approaches

Chronic rhinosinusitis (CRS) is characterized by a complex pattern of inflammation that differs considerably between CRS with nasal polyps (CRSwNP), CRS without nasal polyps (CRSsNP) and CRSwNP accompanying cystic fibrosis (CF-CRSwNP).

In CRSwNP tissue the frequency of eosinophils, B-cells, T-cells, macrophages, neutrophils and dendritic cells is enhanced and these cells orchestrate, although not mutually exclusively, a T helper 2 (Th2) dominated inflammatory response. IL-5, IL-13, IL-25, thymic stromal lymphopoietin (TSLP) and also IL-32 and IL-33 are up-regulated in CRSwNP tissue. Th2-cells and type 2 innate lymphoid populations (ILC) significantly contribute to IL-13 and IL-5 production. Moreover, eotaxins, leukotrienes and prostaglandins are released by mast cells and eosinophils or basophils. Upon inflammation and exposure to infectious or non-infectious trigger factors like allergens, IL-33, IL-25 and TSLP are either secreted (IL-25, TSLP) or released upon cell damage (IL-33). These cytokines are capable to activate residing ILCs, that boost IL-13 and IL-5 production and further up-regulate Th2-driven inflammation and activate effector cell types. IL-4 and IL-13 promote isotype switching of resident B-cells to generate local IgE with specificity to Staphylococcus endotoxin B (SEB) and other, not yet specified antigens, which could be relevant trigger factors that contribute to chronic inflammation. In addition chemokines that favor immune cell recruitment (CCL11, CCL18, CCL24, CCL26) and inflammatory cytokines like IL-6, IL-8 and TNFα are up-regulated in CRSwNP and enhance local inflammation (Figure 1).

The heterogeneity according to environmental factors is underlined by data from nasal polyp tissue from a Chinese population. In this subgroup, inflammation is neutrophil dominated, non-eosinophilic (90%) and devoid of IL-5 protein and more aligned with a Th1/Th17-type response, with increased expression of IFNγ, IL-1ß, IL-6 and IL-17A.

CRSsNP is characterized by an increased production of Th1/Th0-associated cytokines (IFNγ), increased expression of TGF-ß1 and TGF-ß2 receptors on effector cell populations and an up-regulation of the TGF-ß pathways, which is in accordance with typical features, such as fibrosis, basement membrane thickening, goblet cell hyperplasia, sub-epithelial mononuclear inflammation and edema (Figure 2).

CF-CRSwNP can be considered an entity of its own characterized by

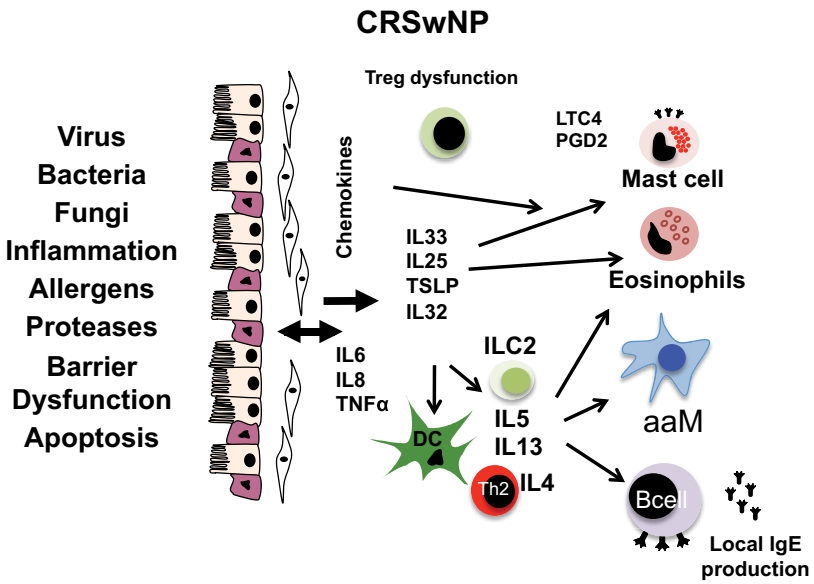

Figure 1 The cytokine network in chronic rhinosinusitis with nasal polyps (CRSwNP). CRSwNP is dominated by a Th2-type inflammatory environment, which is insufficiently controlled by regulatory T-cells. The epithelium releases, either by secretion, or upon cell death and apoptosis, cytokines that activate innate lymphoid cells (ILCs) that produce large amounts of IL-5 and IL-13 in concert with Th2 cells. In addition, a number of chemokines are released that recruit Th2 cells. The Th2 cytokines recruit and activate eosinophils and mast cells, trigger their mediator release, promote local IgE production and activate alternatively-activated macrophages (AAM).

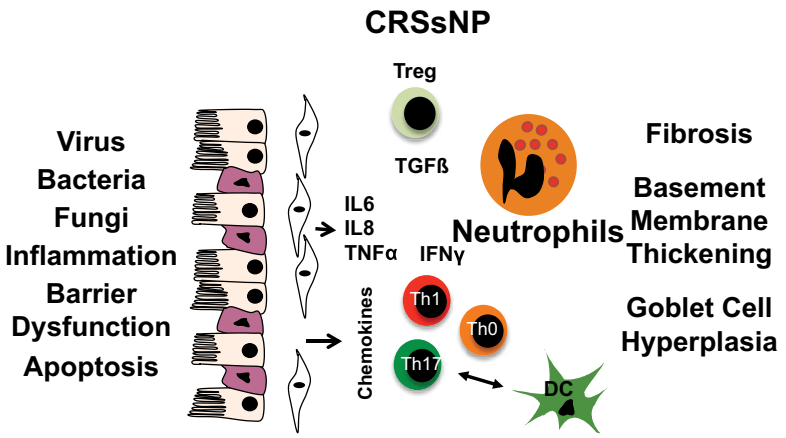

Figure 2 The cytokine network in chronic rhinosinusitis without nasal polyps (CRSsNP). CRSsNP is characterized by an increased production of the T helper 1 (Th1) associated cytokines (IFNγ, TNFα) and an enhanced production of TGF-β, accompanied by a higher expression of TGFβ1 and TGFβ2 receptors on effector cell populations. Moreover, the epithelium significantly contributes to inflammation by enhanced production of IL-6, IL-8 and TNF-α. The frequency of neutrophils is higher in CRSsNP tissue as compared to controls. This leads to typical features like fibrosis, basement membrane thickening and goblet cell hyperplasia.

a neutrophil-mediated inflammation with increased IL-1β, TNFα, IL-8, IL-17A, myeloperoxidase and increased expression of innate defense proteins such as surfactant proteins A, B and D.

Given the broad range of inflammatory mediators involved and the inter-patient variability, it is likely that numerous CRS endotypes exist that need to be defined in the future to generate targeted therapies for CRS patients.

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8 MUCOCILIARY TRANSPORT IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Mucociliary transport is the primary physical defense of the airways against inhaled pathogens and irritants
- Genetic diseases that decrease mucociliary transport are characterized by increased incidences of upper and lower airway infections, including chronic rhinosinusitis (CRS)
- Environmental exposure to toxic substances or pathogens that affect ciliary beating or ion/fluid transport can also result in acquired defects in mucociliary transport
- Stasis of sinonasal secretions and failure to properly clear pathogens is an important part of CRS pathology
- Stimulation of mucociliary clearance an important therapeutic target for CRS treatment

The front line of respiratory defense is the sinonasal cavity, which comes into contact with aerosolized fungal spores, bacteria, and viruses with every breath. However, in most individuals, the airways remain free of pathological infection, largely due to multiple first-line innate immune mechanisms working in concert to defend the sinonasal epithelium. The primary physical defense is mucociliary transport (MCT), a specialized function of the airway epithelium, consisting of two components: mucus production and mucus transport. The airway surface liquid (ASL) lining the airways contains a top layer of mucus gel formed from mucin macromolecules secreted by goblet cells and submucosal glands. Mucins are coated by "sticky" carbohydrates that trap inhaled pathogens and particulates. Below the mucus is a watery periciliary layer (PCL). The lower viscosity of the PCL allows motile cilia (Figure 1) to beat rapidly in a spatially and temporally coordinated manner, transporting the debris- and pathogen-laden mucus toward the oropharynx (throat), where the mucus/pathogen/debris mixture is cleared by swallowing or expectoration (Figure 2). MCT is complemented by secretion of antimicrobial peptides (lysozyme, lactoferrin, cathelicidins, and defensins) and reactive oxygen and nitrogen species (hydrogen peroxide and nitric oxide) that directly kill pathogens. Epithelial cells can also secrete cytokines that recruit immune cells to sites of infection.

The fundamental importance of MCT to airway health is highlighted by two genetic diseases. In cystic fibrosis, a disease of altered ion transport, reduced PCL volume causes overly sticky mucus that severely impairs MCT and results in persistent upper airway infections and often fatal lung infections. Primary ciliary dyskinesia, a genetic multi-organ disorder of cilia dysfunction, also causes severely impaired MCT and chronic airway infections. MCT can also be reduced by exposure to various environmental toxins or pathogens that produce ciliotoxic metabolites.

While multiple causes contribute to the development of chronic rhinosinusitis (CRS), a common pathophysiologic sequela is the ineffective sinonasal MCT, resulting in stasis of sinonasal secretions and subsequent chronic infection and/or persistent inflammation. Studies have suggested that alterations of mucus viscosity, ion transport, or ciliary beating may

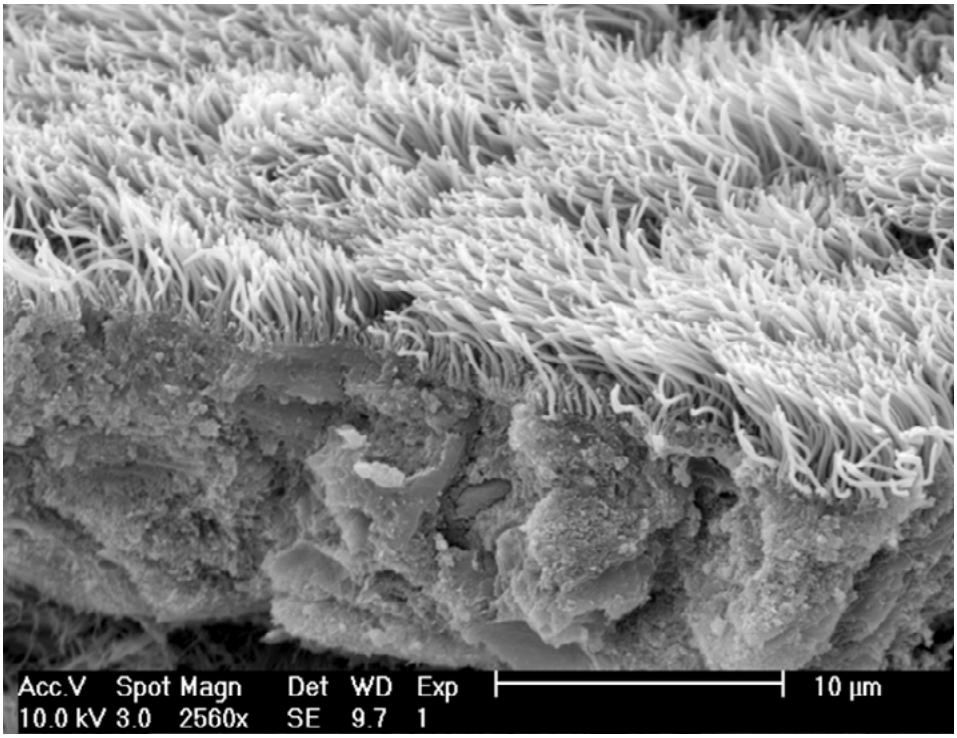

Figure 1 Scanning electron micrograph (SEM) of rabbit maxillary sinus mucosa showing the "carpet" of airway cilia (~7 µm high) found on specialized epithelial cells that line both the upper and lower airway. Paranasal sinus mucosa is made up of predominately ciliated cells, giving the appearance of a shag carpet. Non-ciliated goblet cells are interspersed among the ciliated cells. Goblet cells secrete airway mucin molecules and other protein components of airway mucus.

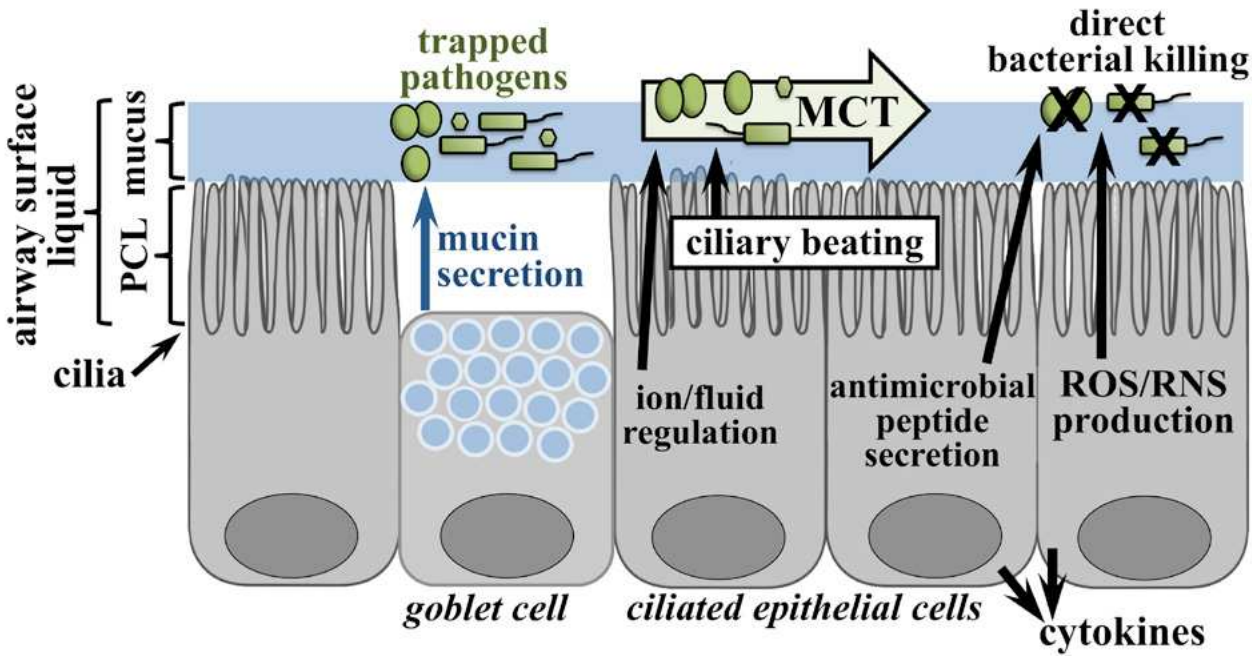

Figure 2 Diagram of mucociliary transport (MCT) intervention in airway innate immunity. Inhaled pathogens are trapped by the sticky mucus layer overlaying the airway surface liquid (ASL). The mucus rides on top of the less viscous periciliary layer (PCL), propelled by the rapid (~8-15 Hz) beating of airway ciliated cells, which affect MCT by both regulating ciliary beat frequency, as well as transporting ions and fluid that affect the composition and viscosity of the PCL. Acquired or genetic defects in ciliary beating and/or ion transport can reduce MCT and lead to increased incidences of airway infections.

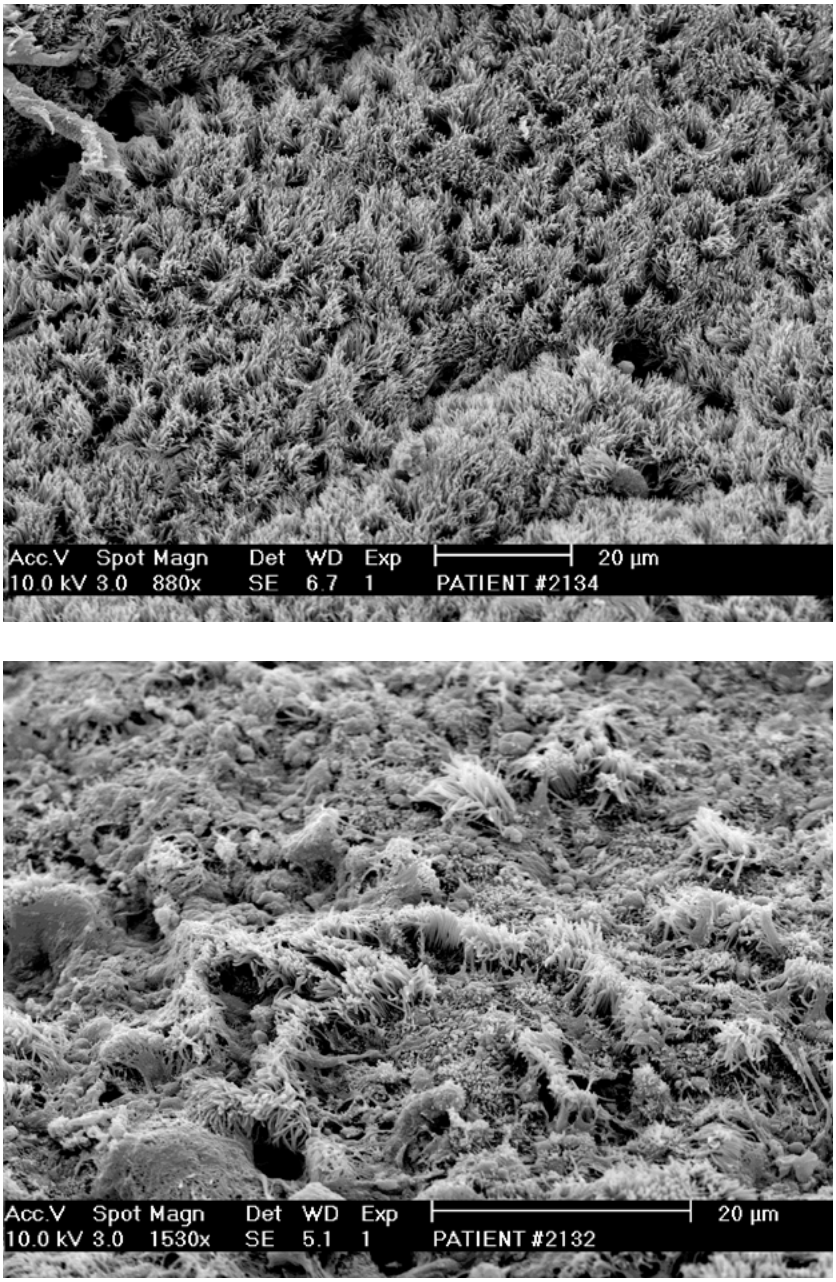

Figure 3 Ciliary loss in CRS. SEMs of sinonasal samples obtained from a normal patient with no sinonasal disease (Left) and a patient with CRS (Right). Note the significant ciliary loss in CRS mucosa with only the stubs of microvilli present. Loss of cilia and epithelial damage in CRS is one mechanism thought to result in decreased MCT and contribute to CRS pathology.

exist in CRS as either genetic or acquired defect (Figure 3). The presence of multiple pathophysiological mechanisms existing under the umbrella of CRS complicates treatment, but it is commonly believed that increasing MCT in CRS patients is likely to be beneficial by promoting pathogen clearance, making the stimulation of sinonasal ciliary function an attractive therapeutic target in CRS.

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9 AIRWAY REMODELING IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Remodeling occurs in the sinuses of patients with chronic rhinosinusitis (CRS) and its pattern is mainly related to the CRS phenotype (with or without nasal polyps), but also probably correlates to the severity of inflammation
- The concept of "dysfunctional sinus", described by various authors as a clinical observation, has no unified definition, and has not been yet linked to remodeling either histologically or ultrastructurally
- It is currently not known whether early steroid intervention in CRS could stop progression into a potentially irreversible state
- Radical surgical procedures that had been described to address dysfunctional sinuses include: Caldwell-Luc and Denker's procedures; maxillary mega-antrostomy or a Draf-3 frontal drillout procedure

Airway remodeling is a broad term used to describe the set of structural modifications that occurs in the airways. It has been noted to occur in the lower airways in asthma. The sinuses in chronic rhinosinusitis (CRS) have also been shown to exhibit features of remodeling (Table 1, Figure 1), described as resembling those of the asthmatic lower airways. The two major clinical CRS phenotypes (CRS without polyps - CRSsNP and with polyps - CRSwNP) exhibit different remodeling patterns, as they exhibit different inflammatory profiles.

The clinical question that has recently been raised is whether recent basic science knowledge about remodeling could alter the management of CRS patients. Current treatment philosophies for CRS revolve around a concept of disease reversibility: steroids are given to reverse inflammation; functional endoscopic sinus surgery (FESS) is performed to relieve ostial obstruction and restore ventilation. Consequently, the occurrence of potentially-irreversible changes in the mucosa challenges this paradigm.

One of the most important potentially-irreversible changes is collagen deposition by myofibroblasts (activated fibroblasts), a process promoted mainly by the action of TGF-β. Collagen deposition cannot be reversed by steroids (although some animal model studies, through measurement of subepithelial basement membrane thickness, suggested otherwise). This knowledge could affect clinical decision making via two means: firstly through the early introduction of steroid therapy to stop the development

TABLE 1

Remodeling features in the sinuses
Epithelial detachment, goblet cell hypertrophy
Myofibroblast accumulation and collagen deposition
Subepithelial basement membrane thickening
Edema, pseudocysts and extracellular matrix deposition → polyp growth
Osteitic changes (neo-osteogenesis or conversely, bone erosion)

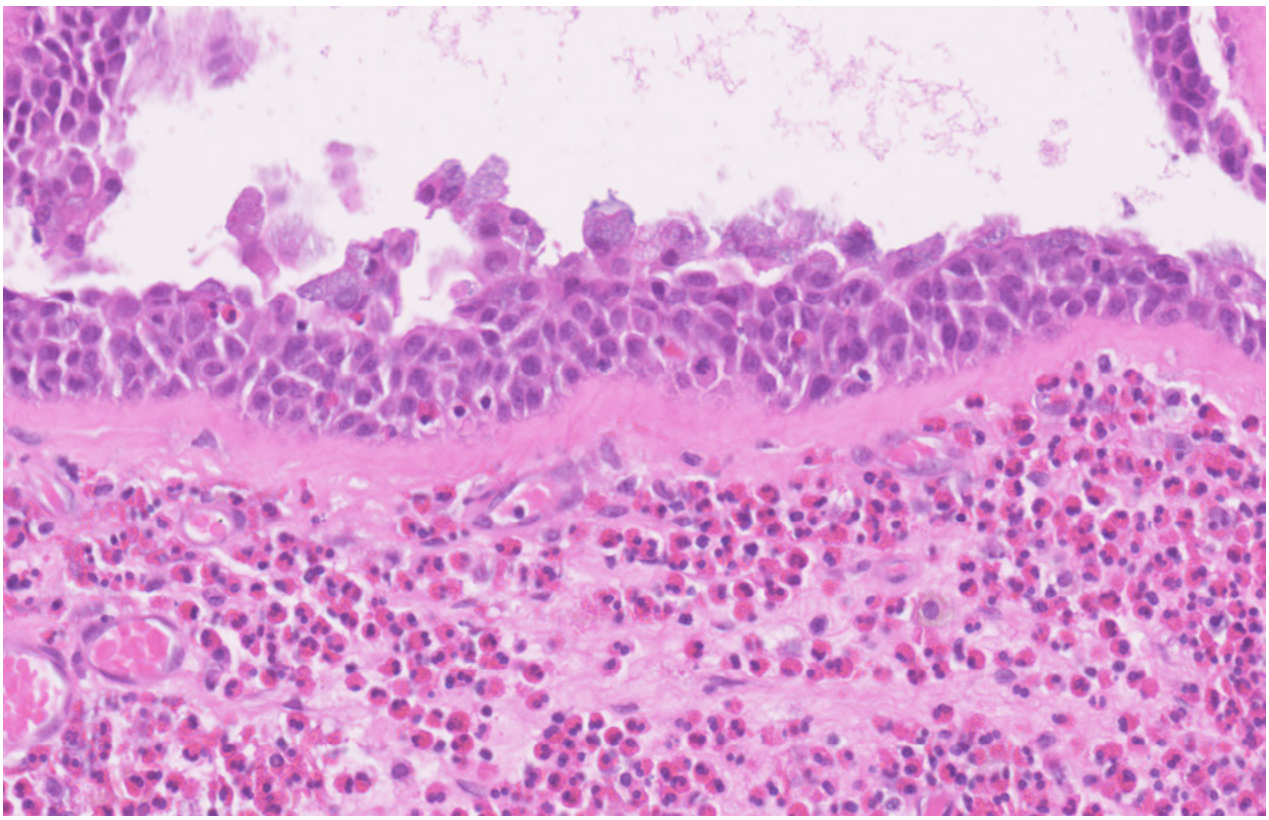

Figure 1 A CRSwNP tissue section showing cross out marked subepithelial basement membrane thickening as well as florid eosinophilia. Evidence from murine model allergen provocation studies suggest a critical role of eosinophils in the remodeling process.

of this irreversible fibrosis; secondly through alternative more extensive surgical techniques. To our knowledge, early intervention with steroids has not been explicitly investigated in CRS. As for the second means, there exists some low-level evidence (in the form of case series reports) for successful radical/extensive procedures to salvage "dysfunctional sinuses" (i.e. sinuses clinically perceived as irreversibly-diseased). The philosophy of these techniques is either a radical removal of dysfunctional mucosa (e.g. Caldwell-Luc or Denker's procedure) or the allowance of gravity-dependent mucociliary clearance through maximal ostium-widening procedures (e.g. mega-antrostomy for a maxillary sinus or a Draf-3 frontal drillout for a frontal sinus). But neither "dysfunctional sinuses" nor the benefit conferred by these techniques have been studied in relation to remodeling, which is a more recently described phenomenon.

In summary, the current level of evidence for a clinical value for remodeling in CRS is low (Level of Evidence: 5). Future studies need to ascertain whether remodeling actually plays a role in influencing the prognosis and/or treatment options. An initial good step is to investigate features of remodeling in a cohort of patients suffering from refractory CRS.

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10 EPIDEMIOLOGY OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Chronic rhinosinusitis (CRS) may affect 5% to 13% of the general population
- Pre-morbid conditions present before the diagnosis of CRS include atopic conditions, recurrent infections, gastro-esophageal reflux disease, sleep apnea, anxiety and headaches
- Co-morbidities associated with CRS include allergic rhinitis, asthma, gastro-esophageal reflux disease, antibody deficiency, aspirin sensitivity, and sinus bacterial biofilms
- In the United States, the annual direct cost for CRS health care is $ 8.6 billion

PREVALENCE AND INCIDENCE

Measuring prevalence of chronic rhinosinusitis (CRS) in the general population is difficult because its symptoms overlap with symptoms of other common conditions such as allergic rhinitis (AR), non-AR and migraine. In addition, there is no distinct biological marker for CRS diagnosis and only a small proportion of patients undergo the objective confirmatory diagnostic tests namely, computerized tomography (CT) scanning of paranasal sinuses and nasal endoscopy. As a result, CRS epidemiological surveys rely on self-report of CRS symptoms (the presence of two or more symptoms for > 12 weeks: nasal congestion, nasal discharge, facial pressure/pain, loss of smell. One of the symptoms must be either congestion, or discharge) and have excluded individuals who report physician-diagnosis of AR. These surveys have detected a prevalence of CRS of 5% to 13% in the United States (U.S.), Europe and China, which may be overestimations due to the absence of confirmation by sinus CT or rhinoscopy.

CRS is most prevalent in adults, because sinuses are not fully formed until adolescence. Median age of diagnosis is 48.4 years for CRS with nasal polyposis (CRSwNP) and 40.3 years for CRS without nasal polyposis (CRSsNP). Prevalence rates peak between 35 and 64 years of age, and 20% of CRS patients have nasal polyps (NP). Males account for 54% of patients with CRSwNP and 42% of those with CRSsNP.

The incidence rates of CRSwNP and CRSsNP in a primary care population in the United States were 83 and 1,048 cases per 100,000 person-years, respectively. Patients with CRSwNP were older and more likely males compared with CRSsNP.

PRE-MORBID CONDITIONS

The cause of CRS is unknown. Pre-morbid conditions (Table 1) present before the onset of CRS may reveal clues to the pathogenesis of the disease in the future. Prior to diagnosis of CRSsNP, patients experienced increased prevalence of infections of the respiratory tract, skin/soft tissue, and urinary tract compared to the general population. Before the initial CRS diagnosis, patients also have greater number of visits to physicians and of antibiotic prescriptions.

CO-MORBIDITIES

Patients with CRS may suffer several co-morbidities (Table 2). Those with CRSwNP have a higher prevalence of atopic conditions than those with CRSsNP.

Subtypes of CRS include eosinophilic CRS, allergic fungal rhinosi-

TABLE 1

Pre-morbid conditions before chronic rhinosinusitis (CRS) diagnosis	
• Acute sinusitis	• Otitis media
• Allergic rhinitis	• Adenotonsillitis
• Chronic rhinitis	• Skin infections
• Asthma	• Sleep apnea
• Atopic dermatitis	• Anxiety
• Conjunctivitis	• Headaches
• Gastroesophageal reflux disease	

TABLE 2

Co-morbidities associated with CRS	
• Allergic rhinitis	• AERD
• Asthma	• GERD
• Atopic dermatitis	• Antibody deficiency
• Eosinophilic CRS	• Cystic fibrosis
• AFRS	• Sinus bacterial biofilms

Abbreviations: AFRS: allergic fungal rhinosinusitis AERD: aspirin-exacerbated respiratory disease. GERD: Gastroesophageal reflux disease.

TABLE 3

CRS health care utilization and costs per year in the U.S.
• 250,000 sinus surgeries
• 11.1 million medical visits
• 5.67 workdays missed/patient
• 7.1% of all adult outpatient antibiotic prescriptions
• $ 8.6 billion in direct cost
• Among the top 10 most costly conditions in the U.S.

nusitis (AFRS), and aspirin-exacerbated respiratory disease (AERD). AFRS can be present in 0-23% of all CRS patients with higher prevalence in warm and humid geographic regions, and also among the young, African Americans, and those of low socioeconomic status. AERD may also affect up to 23% of CRS patients, and is more common in women, and those with atopic diseases (asthma and AR).

In tertiary medical care centers, antibody deficiencies have been identified in up to 22% of adult CRS patients and up to 50% of children with CRS, and more so in those with CRSwNP. These deficiencies are mainly functional antibody deficiencies, selective IgG deficiency and common variable immunodeficiency. Children with cystic fibrosis are also at risk of developing CRSwNP.

Other co-morbidities include asthma, sinus mucosal bacterial biofilms, and aspirin sensitivity. Asthma is more prevalent in patients with CRSwNP and women, a combination often associated with severe forms of asthma.

HEALTH CARE COST AND UTILIZATION

CRS is associated with a large health burden to the patient and society (Table 3). It costs several billion dollars annually in direct health care costs in the United States. Patients with CRS miss a number of workdays similar to those experiencing an acute asthma episode (5.79 days/year). Out of pocket expenses for patients with CRS are greater than that of patients with chronic bronchitis, asthma, or AR. About 50% of all sinus surgeries performed in CRS are nasal polypectomies. Up to 69% of polypectomies are repeat surgeries because NP often recur.

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11 RISK FACTORS FOR CHRONIC RHINOSINUSITIS

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Chronic rhinosinusitis (CRS) with (CRSwNP) or without nasal polyps (CRSsNP) has a broad spectrum of associations ranging from genetics to comorbid diseases and environmental factors (Figure 1). Differentiation of risk factors from comorbidities remains difficult due to variable disease definitions, lack of longitudinal studies to establish temporal relationships between exposure and disease onset and difficulty in the evaluation of the dose-effect size on the disease severity.

KEY MESSAGES

- Distinguishing risk factors for chronic rhinosinusitis (CRS) from comorbidities remains difficult
- Allergy and asthma are regularly found as comorbid diseases and have been considered in several studies as risk factors of CRS
- Autoimmune inflammatory diseases or immune deficiencies should also be considered as potential disease modifiers in CRS
- Anatomical nasal or sinus abnormalities have regularly been suspected in the development of CRS, even strong evidence is lacking
- Environmental and occupational factors could also influence the development of inflammation of the paranasal cavities

CILIARY IMPAIRMENT

Patients with Kartagener's syndrome, primary ciliary dyskinesia, and cystic fibrosis have frequently a long history of CRS.

ALLERGY

Considering its frequent association with CRS and its similar increasing prevalence, atopy has been suspected to predispose to CRS, because the swelling of the nasal mucosa in allergic rhinitis may compromise ventilation at the site of the sinus ostia and, additionally, the sinus inflammation could be induced through a local extension from the initial nasal inflammation.

ASTHMA

In a recent study on over 52,000 adults, GA^{2}LEN researchers concluded that there was a strong association of asthma with CRS. In another study, a highly significant and independent correlation was noted between the extent of disease and the peripheral eosinophil count, presence of asthma and of atopy.

ASPIRIN SENSITIVITY

In patients with aspirin sensitivity, up to 90% have CRS with radiographic changes. Patients with aspirin sensitivity, asthma and CRSwNP are usually non-atopic.

IMMUNOCOMPROMISED STATE

Dysfunction of the immune system such as abnormal T-lymphocyte proliferation or selective immunoglobulin deficiencies may be associated with CRS.

AUTOIMMUNE AND OTHER INFLAMMATORY DISEASES

Chronic granulomatous diseases may require extensive pharmacologic and surgical treatment for their associated CRS.

GENETIC FACTORS

Although CRS has been observed in family members, no genetic background has formally been identified as to be linked to CRS.

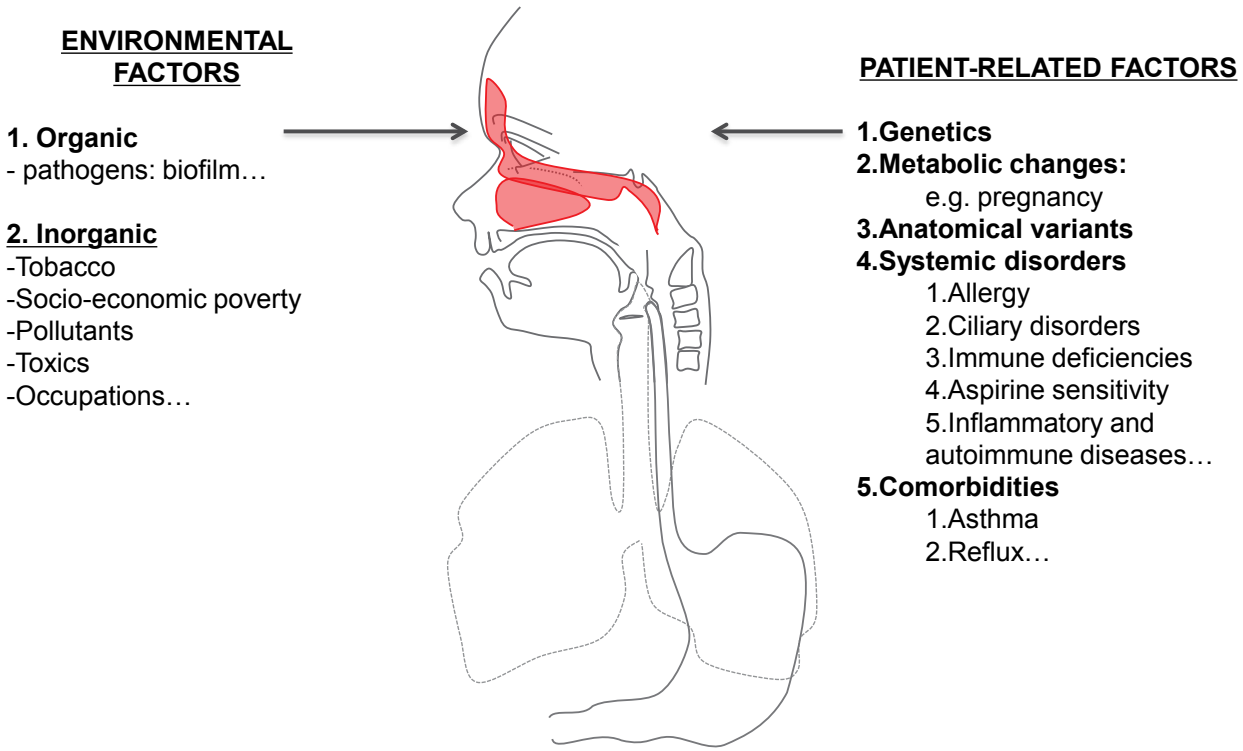
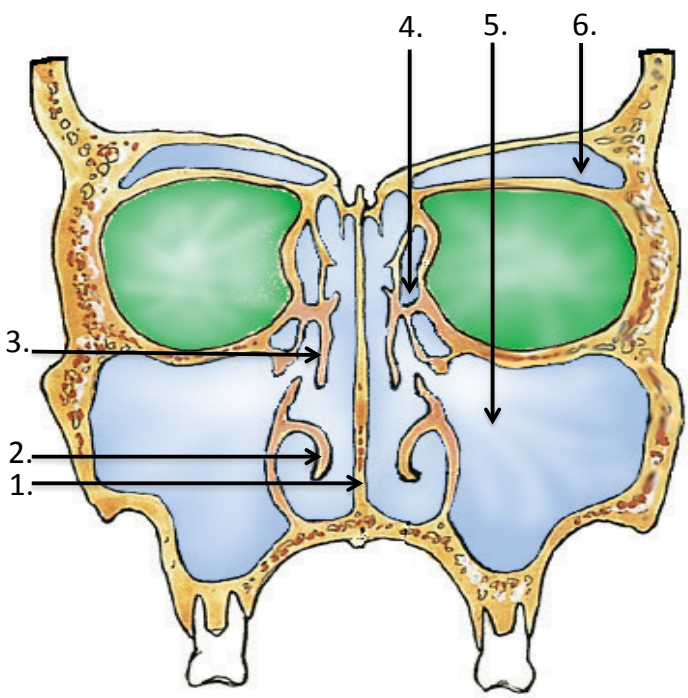


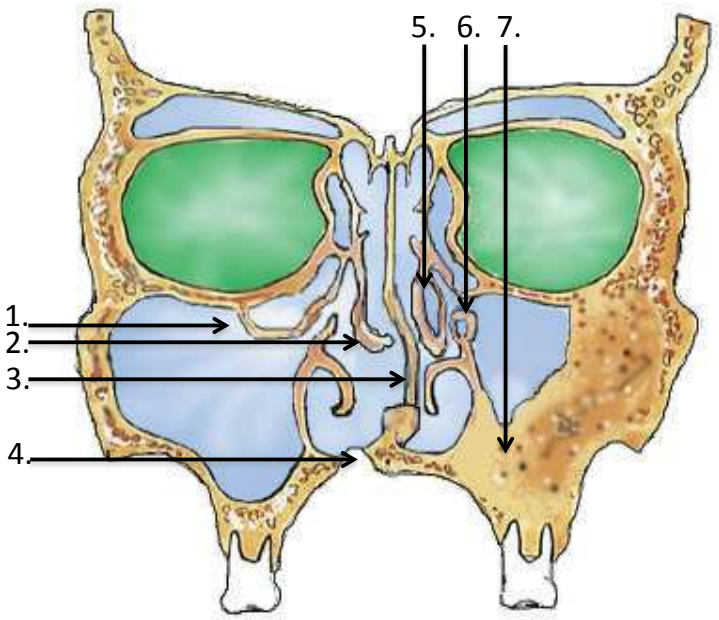
Figure 1 Major risk factors and comorbidities for chronic rhinosinusitis.



LEGEND:
1. Nasal septum
2. Inferior turbinate
3. Middle turbinate
4. Ethmoid sinus
5. Maxillary sinus
6. Frontal sinus

Figure 2 Normal anatomy of the nasal and paranasal cavities.

'atelet JB, MD, PhD



LEGEND:

1. Haller cell
2. Paradoxical middle turbinate
3. Septal deviation
4. Oronasal fistulas
5. Cocha bullosa
6. Pneumatized uncinate process
7. Hypoplastic sinus

Figure 3 Examples of spontaneous or iatrogenic anatomic variants having been suspected to induce CRS.

LOCAL ANATOMICAL FACTORS

Although some authors have suggested that spontaneous or iatrogenic anatomical variations of the paranasal sinuses or nasal structure (Figures 2-3) can contribute to ostial obstruction, there are several studies that show the prevalence of anatomical variations is not more common in patients with CRSsNP or CRSwNP than in controls.

ENVIRONMENTAL FACTORS

Cigarette smoking was associated with a higher prevalence of CRS in European countries. Other lifestyle-related factors can be involved in CRS such as low income, pollutants, toxins, occupations as plant or machinery operators, crafts, even if their precise role in CRS pathogenesis remains unclear.

GASTRO-, LARYNGO-PHARYNGEAL REFLUX

There is not enough evidence to consider acid reflux as a significant causal factor in CRSsNP.

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12 CLASSIFICATION OF CHRONIC RHINOSINUSITIS

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Chronic rhinosinusitis (CRS) in adults is defined as inflammation of the nose and the paranasal sinuses producing ≥12 weeks of symptoms without complete resolution. It is characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), ± facial pain/pressure, ± reduction or loss of smell. In a specialist/ENT setting, CRS diagnosis is supported by endoscopic signs of nasal polyps, and/or mucopurulent discharge primarily from middle meatus, and/or oedema/mucosal obstruction primarily in middle meatus and by computer tomographic (CT) findings such mucosal changes within the ostiomeatal complex and/or sinuses.

In children CSR is defined as for adults except that cough replaces reduced or loss of sense of smell. Both adults and children CRS may be classified based on the visual analogue scale (VAS) score (0 - 10cm) as mild (VAS 0-3), moderate (VAS between 3-7) or severe (VAS >7) (Figure 1). Further classifications of CRS have included anatomical features, inflammation or co-morbidities (Table 1). These have led to a closer consideration of endotyping and phenotyping CRS to facilitate its classification.

KEY MESSAGES

- A simple generic approach has been adopted to the classification and definition of chronic rhinosinusitis to facilitate its diagnosis in a range of clinical settings
- A combination of symptoms and their duration remain the mainstay, confirmed by endoscopic appearances and/or imaging
- Further classification relies on the presence or absence of nasal polyps, inflammatory profiling and co-morbidities

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TABLE 1

Criteria used for the classification of chronic rhinosinusitis
• The presence or absence of nasal polyps (NP) on endoscopic examination: CRS with NP (CRSwNP) and withouth NP (CRSsNP), which is a pragmatic choice of classification, largely reflecting the literature on management
• The predominance of eosinophils or of other inflammatory cells on histologic examination of sinonasal tissue
• Cytokine and other mediator profiling
• The presence or absence of co-morbidities eg asthma, aspirin exacerbated respiratory disease, cystic fibrosis

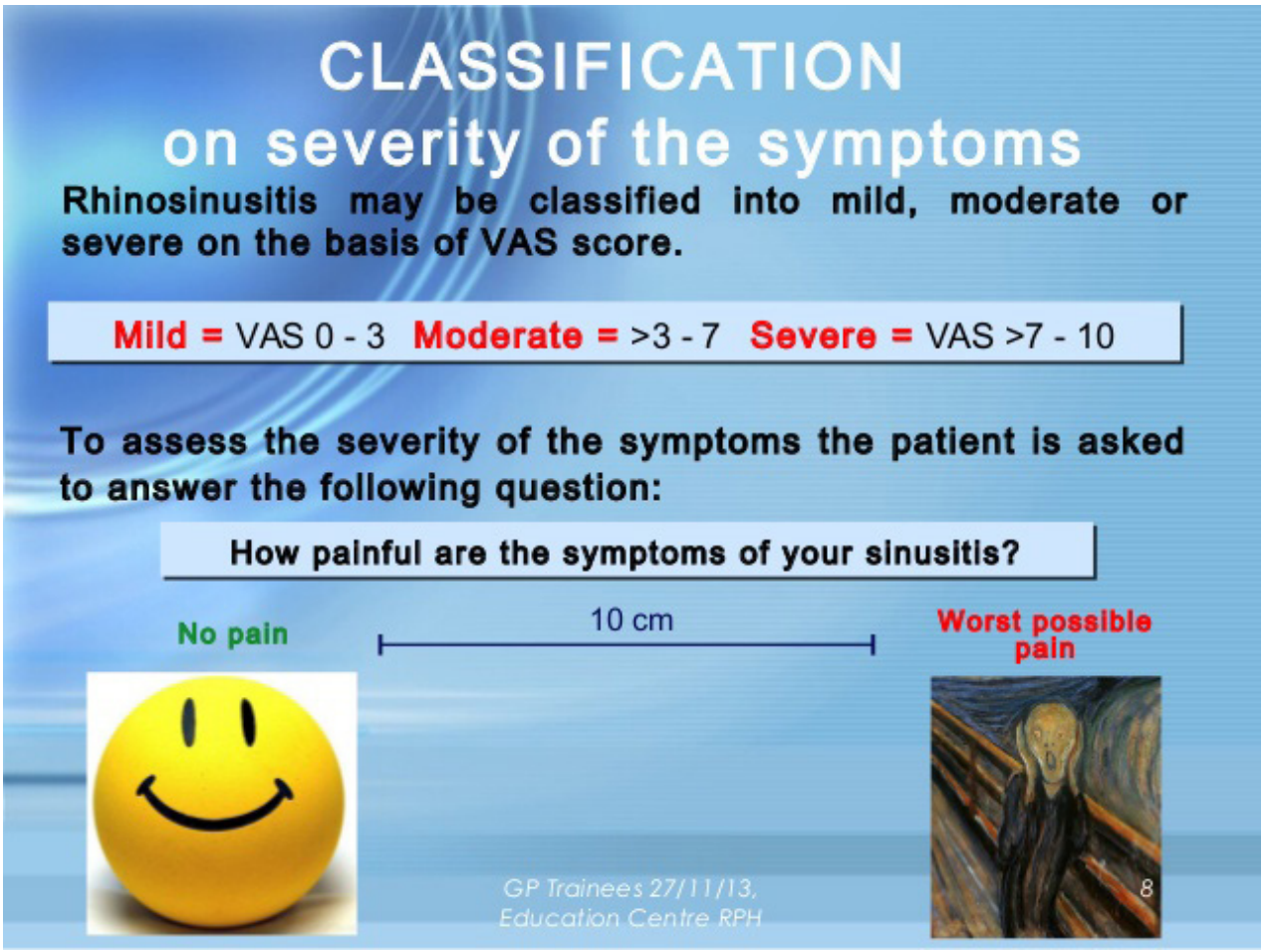

Figure 1 Evaluation of the severity of chronic rhinosinusitis using the visual analogue scale score.

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13 CLINICAL FEATURES OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Loss of smell is a strong positive predictive factor for the presence of mucosal inflammation in chronic rhinosinusitis (CRS) and is uncommon in simple rhinitis
- Significant facial pain as a dominant presentation is rare. Inflammation of mucosal surfaces that produces pain also produces significant other sino-nasal symptoms
- Infective exacerbations of CRS usually last at least 1-2 weeks. Flare-ups that last only several days are likely to be rhinitis and not rhinosinusitis
- Cough and other regional symptoms such as dysphonia are more likely to represent broader airway involvement in a chronic inflammatory process than direct effects of sinus disease

The presenting symptoms of chronic rhinosinusitis (CRS) are broad. However, four cardinal features are often present: nasal congestion, nasal discharge, facial pressure and loss/distortion of smell. These are the 'local' symptoms of chronic sino-nasal disease (Figure 1). Regional symptoms include Eustachian tube dysfunction, cough, post-nasal drip and dysphonia. Although, these symptoms can be a result of direct irritation from secretions, they are more likely to represent broader involvement of the airway in the associated disease process. When it comes to chronic disease, compartmentalization of airway symptoms (upper, lower, middle) is the exception rather than the rule. Systemic features include malaise and minor depression.

The local features are important and current diagnostic criteria need to include the presence of nasal congestion or discharge with either pressure or smell loss in the setting of endoscopic or radiological evidence of mucosal inflammation (Figure 2).

Nasal congestion is very ambiguous and the term nasal obstruction is often avoided as the question is raised as to why is the nose blocked, if the inflammatory condition is primarily in the sinuses? Although concomitant rhinitis can exist, this nasal congestion is seen even in simple localised forms of CRS (infected fungal ball, odontogenic CRS). Along with the vasodilation that can occur from nearby inflammation, there is an ipsilateral nasal reflex with induced vascular dilation in response to sinus stimulus. Thus, congestion is often used to describe this symptom in CRS, outside the direct involvement of the nasal cavity with nasal polyps.

Nasal discharge is a common feature in the setting of CRS. Anterior mucoid discharge is common in inflammatory disease and is often green in appearance. The green pigment of mucus comes from the iron containing heme groups of myeloperoxidase. Myeloperoxidase comprises 5% of the dry weight of polymorphonuclear cells and it accumulates in absence of bacteria, rarely implying infection. Cachosmia associated with discharge is common feature of CRS of odontogenic origins and signals true bacteria contribution. Sticky or 'chewing gum' mucus is a common feature of eosinophilic conditions that are associated with degranulated eosinophil products in mucin.

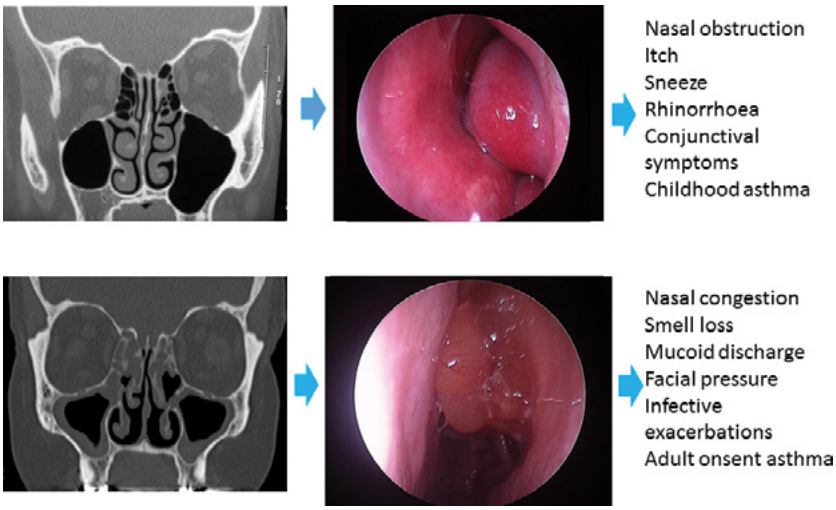

Figure 1 The constellation of presenting symptoms between rhinitis and chronic rhinosinusitis (CRS) can at first appear very similar. However, the nasal obstruction (congestion) and rhinorrhoea (mucoid discharge) of rhinitis differ to CRS due to the underlying pathophysiological process in the sino-nasal cavity.

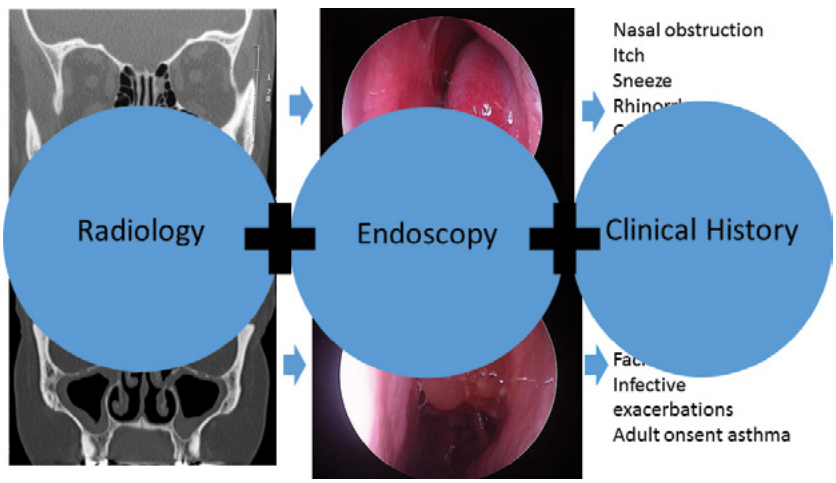

Figure 2 The accurate diagnosis of chronic rhinosinusitis involves a combination of symptoms with features of inflammation on endoscopy and radiology. The use of symptoms alone has a poor specificity even with specialist assessment.

Facial pressure is a major feature of CRS, but it is rarely true facial pain. CRS is inherently a mucosal inflammatory condition and the presence of facial pressure (pain) needs to be proportionate to other symptoms that should exist if significant mucosa-based inflammation were present. This is the basis for facial pain not being a primary presentation of CRS. If mucosal inflammation was causing significant pain, then it is axiomatic that other non-pain based symptoms would be present (congestion, discharge). Patients with facial pain as major presenting complaint rarely have CRS as the cause. Loss or distortion of smell is a common finding in CRS, but not in rhinitis. Olfaction is sensitive to mucosal oedema (due to vascular congestion) and is a strong predictive factor for CRS.

Finally, for CRS patients, the disease burden and impact on quality of life is high. Although not life-threatening, it causes loss of productivity, accounts for a significant proportion of presentations to primary care physicians and results in a large health expenditure cost.

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14 ENDOTYPES AND PHENOTYPES OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Chronic rhinosinusitis (CRS) has a variety of overlapping phenotypes and endotypes
- CRS with nasal polyps may have an eosinophilic or neutrophilic pathogenesis, but the clinical appearance of polyps is similar in both
- Systemic diseases other than allergy are also associated with CRS
- Sampling at multiple nasal or sinus mucosal sites may show variability of endotypic markers, suggesting that the various endotypic categories share characteristics or are heterogeneous
- Treatment of CRS would be improved with endotypic specific or directed therapy

The accurate characterization of the endotypes (pathogenic mechanism) and of phenotypes (physical or clinical manifestations) of chronic rhinosinusitis (CRS) requires a precise diagnosis, specific characteristics that are clinically identifiable and distinct pathogenetic mechanisms. Unfortunately, these requirements generally are not clearly fulfilled for CRS.

CRS is defined as 12 weeks of documented disease. However, the duration is difficult to verify as the onset of disease may not be recognized. The clinical criteria for CRS overlap with the more common forms of rhinitis and among the subtypes of CRS (Table 1). Most forms of chronic rhinitis increase the likelihood of CRS since the sinus mucosa is contiguous with the nasal mucosa; therefore, there is overlap among the disease mechanisms for rhinitis and CRS. The typical symptoms of rhinosinusitis, which help define the phenotype, are nonspecific and overlap with rhinitis. Recurrent acute rhinosinusitis (3 or more episodes per year) may be confused with CRS. Finally, sinusitis is often diagnosed clinically, which may result in over- or under-diagnosis. Ideally endoscopy or paranasal CT imaging should confirm the diagnosis, if CRS is suspected. Thus, the clinical features of CRS limit the ability to accurately phenotype and endotype the disease.

CRS has multiple causes (Figure 1) and the partial ability to precisely identify causal mechanisms reduces the likelihood to define the endotype (underlying pathobiologic mechanism), and to recognize the unique phenotypic characteristics. The CRS phenotypes generally accepted are presented in Table 2. These categories are not mutually exclusive. For example, the CRS associated with allergic rhinitis (CRSwAR) may develop into eosinophilc CRS with

TABLE 1

Typical symptoms of chronic rhinitis and sinusitis
Symptoms of chronic rhinitis
• Rhinorrhea
• Nasal congestion
• Sneezing (less for chronic disease)
• Post-nasal drip
Symptoms of chronic sinusitis
• Hyposmia/Anosmia
• Nonspecific facial discomfort
• Fatigue
• Cough with post-nasal drip and throat clearing

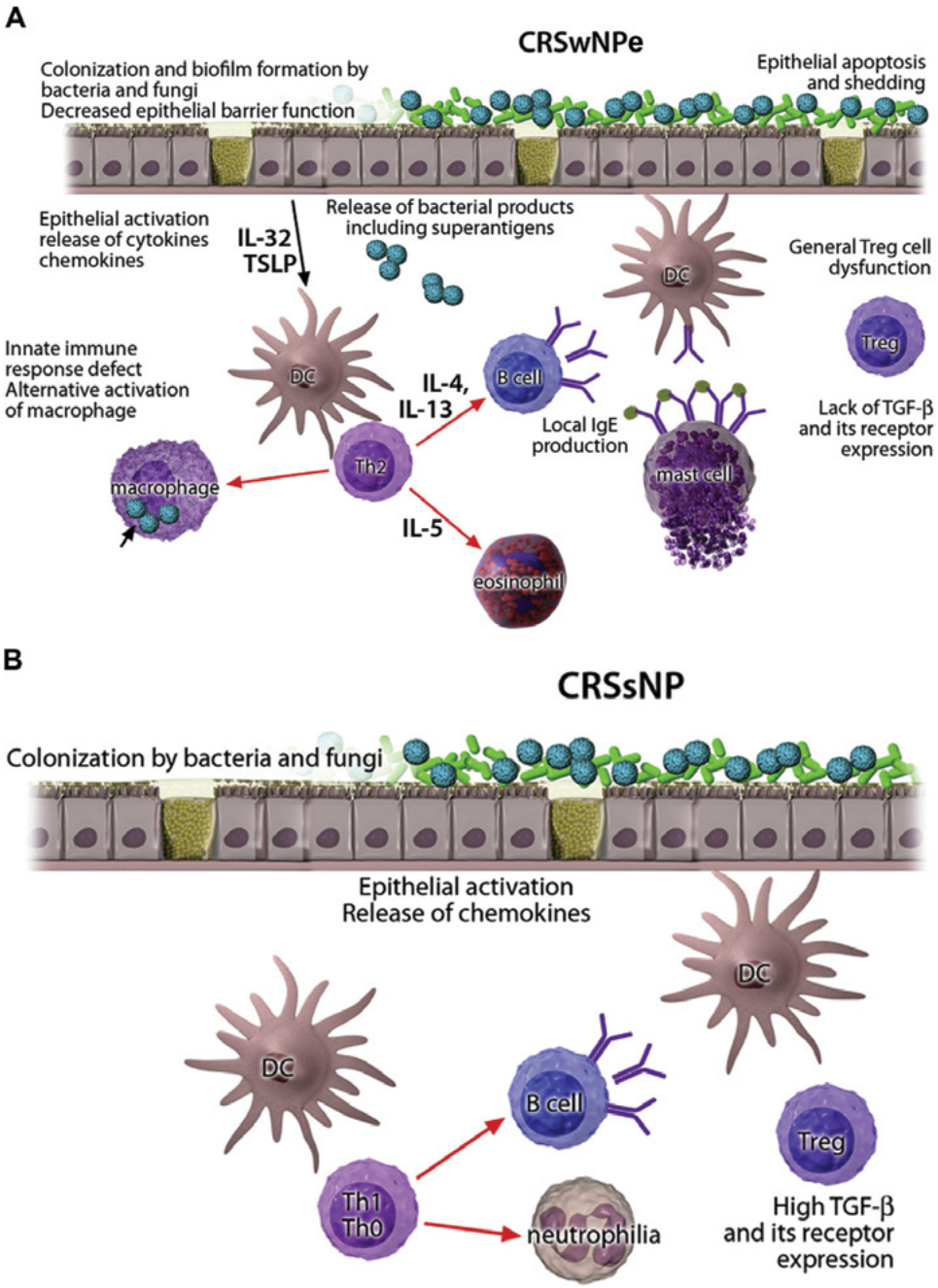

Figure 1 Pathogenic mechanisms of chronic rhinosinusitis, contrasting chronic rhinosinusitis with eosinophilic nasal polyps (CRSwNPe) [Panel A] and chronic rhinosinusitis without nasal polyps (CRSsNP) [Panel B]. Panel A. CRSwNPe in a Th2-type microenvironment with general lack of regulatory T cell (Treg) function, increased interleukin-5 (IL-5) with eosinophilia and increased IL-4 and IL-13 with resulting increased IgE production. Epithelial activation, possibly related to colonization with certain bacteria or fungi, results in the in release of proinflammatory and regulatory cytokines and chemokines such as thymic stromal lymphopoietin (TSLP) and IL-32. Activation and apoptosis of epithelial cells result in compromise of epithelial barriers and increased susceptibility to irritants and infectious agents. Panel B. In chronic rhinosinusitis without nasal polyps (CRSsNP), a Th1 or a mixed Th0 and Th1 response predominates rather than Th2. The result is an increase in mucosal neutrophils and expression of TGFβ and its receptors. (DC: dendritic cells). (*Adapted from Akdis CA, Bachert C, et al. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2013;131:1479-1490.*)

TABLE 2

Phenotypes and endotypes of chronic rhinosinusitis (CRS)

Phenotype Characteristics	Endotype Characteristics		Treatment Implications
Chronic allergic rhinitis with sinusitis (CR-SwAR)	Eos ++ IL-4, 5,13 ++ IL-17, IFN-γ (--)	Th2++ Systemic s-IgE+++	Allergen avoidance or IT INCS and INA Antibiotics ?Omalizumab
Nasal polyposis with rhinosinusitis and mucosal eosinophilia (CRSwNPe)	Eos+++ Edematous polyps++++ IL-4, 5,13+++ IL-10 (-) LT++++*	M2 macrophages++ Th2++ SA/SE/SPA++ ? Local s-IgE+ TGF-β (--) Treg(-)	High dose INCS or OCS LMA Surgery ASA desensitization & therapy* ?Omalizumab ??Mepoluzimab, reslizumab
Nasal polyposis with rhinosinusitis and mucosal neutrophilia (CRSwNPn)	Eos (-) INF-γ++ IL-5 (--) IL-17+	PMN+++ Th1++ Th17++	INCS Surgery ?Macrolide antibiotics
Chronic rhinosinusitis without nasal polyposis (CRSsNP)	Collagen++ PMN+++ SA/SE/SPA+	Th1++ TGF-β+ Treg++	INCS
Allergic fungal hypersensitivity rhinosinusitis (AFRS)	Eos+++ Fungal culture or histology++++ s-IgE++ Total IgE++++		OCS INCS ??Antifungals ???Omalizumab
Chronic rhinosinusitis associated with other systemic diseases	Varies With Disease • Eos++ and ANCA++ (EGPA) • PMN+++ and ANCA+++ (GPA) • PMN ++ with Culture ++ (ID) • CFTR mutation++++ (CF) • Mucosal granulomas (Sarcoid) • Ciliary dyskinesia • ANA/SSA/SSB++ (Sjögren's)		OCS Immunosuppressives Immunomodulators Antibioitcs Gamma globulin replacement

**Aspirin intolerant subjects (Aspirin Exacerbated Respiratory Disease [AERD]).*
Eos: Eosinophils; ASA: Aspirin; +: Increased; IL-4: Interleukin 4; INCS: Intranasal corticosteroid; PMN: Neutrophils; IL-5: Interleukin 5; OCS: Oral corticosteroid; (-): Decreased; s-IgE: Allergen specific-IgE; LT: Leukotrienes; LTM: Leukotriene modifiers; INA: Intranasal antihistamine; LMA: Leukotriene modifiers; ID: immunodeficiency; M2 macrophages: Macrophage subpopulation more involved in Th2 repsonses; Treg: Regulatory T lymphocytes;?: Limited, negative or conflicting data; SA/SE/SPA: Staphylococcal aureus colonization or infection and nasal detection of enterotoxins and staphylococcal protein A; ANCA: Antineutrophil cytoplasmic antibody; ANA/SSA/SSB: Antinuclear antibody with or without specific antibody to SSA and/or SSB; EGPA: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis); GPA: Granulomatosis with polyangiitis (Wegener granulomatosis); CF: Cystic fibrosis; CFTR: Cystic fibrosis transmembrane conductance regulator; Sarcoid: Sarcoidosis; Sjögren's: Sjögren's disease or syndrome

fungal hyphae (AFRS) or possibly CRS with nasal polyps (CRSwNP). Also, allergic fungal rhinosinusitis (AFRS) may demonstrate eosinophilic nasal polyps (NP). Distinct phenotypes, for example CRSwNP and AFRS, may represent distinct diseases or different manifestations of a disease spectrum, that may change from one to another. Furthermore, the apparent endotype of mucosal inflammation, as recognized by selective cell activation and/or cytokine profile, may vary with different mucosal samples from the same individual. Thus, the inflammatory response, which reflects the genetic and environmental interaction, may not be clearly distinguishable. The characteristics of mucosal inflammation often may not be recognized until surgical specimens are histologically and biochemically studied.

CRS is often treated by surgery, particularly for asymmetric disease or obstructive NP. However, CRS is usually a medical condition and successful outcomes invariably require adequate medical evaluation and pre- and post-operative therapy. Clinically useful sampling methods, other than surgery, are needed to better facilitate endotypic characterization. Bacterial infection, other than staphylococcal colonization with endotoxin and protein A production is not generally important to the pathogenesis of CRS, but could exacerbate CRS. Finally, multiple systemic diseases may have CRS as a component of the condition, and the endotypes of these forms of CRS are different, even though the phenotypic presentation may be similar (Table 2).

Pathogenic mechanisms associated with each of the CRS phenotypes are not universally ac-

TABLE 3

Basic clinical tools to characterize chronic rhinosinusitis (CRS) endotypes and phenotypes
History (onset, sense of smell, association with allergens, family history)
Testing for specific-IgE
Fiberoptic or rigid (generally used by surgeons) rhinolaryngoscopy
Mucosal cytology
Paranasal sinus imaging
Nasal/sinus culture
Peripheral blood eosinophil count
Total IgE
Total IgG

TABLE 4

Advanced or research techniques to characterize chronic rhinosinusitis (CRS) endotypes
Surgical histology
Cell subtyping by immunofluorescence or flow cytometry
Cytokine assays from nasal lavage or biopsy
Gene expression
Specific-IgE in nasal or sinus mucosa
Ciliary functional assessment
Antineutrophil cytoplasmic antibody quantification in peripheral blood
Cystic fibrosis genetic testing or sweat chloride test
Bacterial protein expression (e.g. staphylococcal enterotoxin)
Immunologic response to vaccination or *in vitro* immunologic assessment

cepted, although a significant body of research suggests disease mechanisms or potential pathogenetic associations (Table 2). The mechanisms include epithelial barrier abnormalities, selective T cell subpopulation stimulation, local specific-IgE production, selective growth of microorganisms, enhanced leukotrienes and/or prostaglandin concentrations, specific cytokine profiles, and production of factors that regulate fibrosis or cell recruitment such as transforming growth factor beta (TGF-β). Identification of some of these mechanisms has resulted in improved therapeutic approaches or suggestions for more effective therapies (Table 2). The role of infectious agents, very important in acute sinusitis or acute exacerbations of chronic disease, is unclear with difficulties in interpreting culture or genetic identification of infectious organisms due to the possibility of nonspecific or secondary colonization. There is a sizeable literature on the role of *Staphylococcus aureus* in CRSwNP and possibly in CRS without NP (CRSsNP) and fungal organisms in AFRS. Thus, infectious agents are likely important in selecting the endotypes of CRS and definitely for exacerbations of CRS.

Tools generally available to the clinician to phenotype/endotype CRS are listed in Table 3. Research or surgical approaches for CRS characterization or measures of systemic diseases are listed in Table 4. The major limitation in utilizing endotypic assessment of CRS and therapies targeted to disease endotype (Table 2) is the limited availability of cost effective strategies to clinically characterize CRS and the lack of clinical trials of endotypically characterized CRS. The treatment of CRS will likely improve if these barriers to CRS endotyping are overcome.

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15 EOSINOPHILIC CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Eosinophilic chronic rhinosinusitis (ECRS) is a recently described subtype of refractory chronic rhinosinusitis characterized by massive infiltration by eosinophils of the nasal polyps (NP)
- The most prevalent characteristic clinical features of ECRS are strong tendency for recurrence after sinus surgery and the effectiveness of oral (systemic) corticosteroids for the treatment of recurrent NP
- Two-thirds of ECRS patients have asthma, and most are non-atopic with adult onset
- CT findings are useful for the diagnosis, with involvement of the posterior ethmoid sinus and olfactory cleft characteristic for ECRS

Chronic rhinosinusitis (CRS) comprises several subtypes. Most cases of CRS with nasal polyps (CRSwNP) in Western countries have been reported to exhibit eosinophil-dominant inflammation. However, more than half of CRSwNP patients in Japan and East Asia have non-eosinophilic CRSwNP. Until 30 years ago, most individuals with CRS in Japan were shown to exhibit purulent rhinorrhea (including abundant neutrophils). This Japanese conventional CRS was well controlled by the combination of macrolide therapy (long-term, low-dose) and endoscopic sinus surgery (ESS). However, since the 1990s, the number of CRSwNP patients shown to be refractory to the combined therapy has increased gradually. One of the histologic characteristics of the disease is massive infiltration by eosinophils of the nasal polyps (NP). Hence, "eosinophilic chronic rhinosinusitis" (ECRS) has been used to classify this refractory subtype in Japan since 2001.

The most prevalent characteristic clinical features of ECRS are a strong tendency for recurrence after ESS and the effectiveness of oral (systemic) corticosteroids for the treatment of recurrent NP. Clinical features of ECRS in comparison with Japanese conventional CRS are listed in Table 1. Anosmia appears early in the illness and is characteristic for ECRS. While NP are raised from the middle meatus in most non-ECRS patients, ECRS patients can exhibit bilateral NP that are often found in both side of the middle turbinate. Two-thirds of ECRS patients have asthma, and most are non-atopic with adult onset.

CT findings are useful to distinguish ECRS from non-ECRS with involvement of the posterior ethmoid sinus and olfactory cleft characteristic for ECRS. Massive infiltration of eosinophils of NP and eosinophilia in peripheral blood are also characteristics of ECRS.

Eosinophilia in tissue and peripheral blood are closely correlated in most patients. Gene-expression studies have revealed the unique pathophysiologic features of ECRS compared with non-ECRS. From these characteristic features we proposed a diagnostic procedure for ECRS (Table 2). A multicenter study is underway for the definition and diagnostic criteria of ECRS in Japan.

CRSwNP with allergic rhinitis (AR) is often confused with ECRS. They both have eosinophilic infiltration

TABLE 1

Comparison Between ECRS and Japanese conventional CRS

	Eosinophilic Chronic Rhinosinusitis (ECRS)	Japanese conventional chronic rhinosinusitis (CRS)
Characteristic symptoms	Reduction/loss of smell in early stages	-
Endonasal findings	Bilateral polyps, high viscous secretion	Mucopurulent discharge, nasal polyp in middle meatus
CT findings	Ethmoid predominance (in early stages)	Maxillary predominance (in early stages)
Hematology	Eosinophilia	–
Coexistence of asthma	Frequent	Less frequent
Macrolide therapy	Not effective	Effective
Prevalence of recurrence of nasal polyps	Very high	Low
Systemic corticosteroids for recurrence	Higher efficacy	Not known
Histology of nasal polyps	Eosinophilia, lymphocyte infiltration, thickening of basement membrane (remodeling)	Lymphocyte infiltration, increase in number of nasal glands

TABLE 2

Diagnosis of eosinophilic chronic rhinosinusitis

(1) Clinical history

- Symptoms of chronic rhinosinusitis
- Reduction and/or loss of the sense of smell in the early stages

(2) Endonasal examination

- Bilateral polyps
- High viscous secretion

(3) Paraclinical examinations (sensitivity = 0.846; specificity = 0.923)

- Eosinophilia in peripheral blood
- CT findings (posterior ethmoid score ≥ 1, olfactory cleft score ≥ 1, graded according to the Lund-Mackay system)

(4) Postoperative course

- Strong tendency to recur after endoscopic nasal surgery (ESS)
- Effectiveness of systemic corticosteroids for treatment of recurrence

of the NP, but the latter does not always recur after ESS. Therefore, the keyword for ECRS mentioned above is "refractory" and ECRS should be termed "refractory ECRS".

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16 FUNGAL SINUS DISEASE

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The interaction between fungi and the sinonasal tract results in a diverse range of diseases with an equally broad spectrum of clinical severity (Table 1). Fungi are ubiquitous in the environment and accordingly, they are very frequently detected on the nasal mucosa of healthy individuals and their presence only rarely causes disease. The interaction between fungi and nasal mucosa is determined largely by the host immune state. Fungal sinus disease can be divided into non-invasive forms, which are usually seen in immunocompetent patients, and invasive forms usually seen in immunocompromised patients.

KEY MESSAGES

- Fungi are ubiquitous in the environment and their prevalence in the sinonasal tract of healthy individuals has been reported to be as high as 100%
- Fungal rhinosinusitis can be divided into non-invasive forms that are usually seen in immunocompetent patients, and invasive forms that are usually seen in immunocompromised patients
- Treatment of most forms of fungal rhinosinusitis is primarily surgical

BIOLOGY OF FUNGI

The kingdom of fungi encompasses an enormous diversity of organisms from single-celled yeasts to large mushrooms. Moulds are mainly responsible for causing disease in the sinonasal tract and are fungi that grow in the form of multicellular filaments called hyphae. Moulds and their airborne sexual spores or asexual conidia are present in all habitable environments and so human beings inhale them constantly.

NON-INVASIVE DISEASE

Fungal ball are dense accumulations of fungal hyphae within the mucosal confines of a paranasal sinus or sinuses, without tissue invasion (Figure 1). As sinonasal symptoms and clinical signs are either absent or non-specific, the diagnosis is usually made radiologically, and often incidentally, when patients are scanned for non-rhinologic indications. Treatment consists of endoscopic removal of all the fungal content within the involved sinus and the maximal widening of its ostium. There is usually no need for topical or systemic antifungal therapy postoperatively.

Allergic fungal rhinosinusitis (AFRS) is a subtype of chronic rhinosinusitis (CRS) triggered by a hypersensivity reaction to fungi colonizing the sinonasal tract. AFRS is characterized by intense eosinophilic mucosal inflammation. It is unlikely that IgE-mediated hypersensitivity is the major pathogenic factor of this condition and almost certainly other mechanisms of hypersensitivity are involved. AFRS typically affects young, atopic and immunocompetent patients. The resultant CRS with nasal polyposis (NP) is often recalcitrant to conventional treatment. Nasal mucus is characteristically thick, tenacious and coloured from tan to brown or black and is rich in eosinophils or eosinophil degraded products (Figure 2). Severe or neglected cases may present with facial deformity, hypertelorism and proptosis. AFRS has some distinctive radiological appearances both on CT and MRI scanning (Figure 3). The Bent and Kuhn cri-

TABLE 1

Summary of key concepts in most prevalent forms of fungal rhinosinusitis

	Fungal Ball	AFRS	AIFRS
Most common etiologic agent	*Aspergillus* spp	*Aspergillus* spp and dematiaceous molds (*Alternaria* spp, *Bipolaris spp* and *Curvularia* spp)	*Aspergillus* spp and Mucorales (*Rhizopus* spp and *Mucor* spp)
Immune state	Immunocompetent	Immunocompetent Atopic patient	Immunosuspresion (Neutropaenia or neutrophil dysfunction) e.g. hematologic malignancies, organ transplant or diabetic ketoacidosis
Demographics	Most commonly affects middle-aged and elderly females	Warm humid regions e.g. south of North America and India	Inpatient (Usually in critic care units)
Treatment	Surgery	Surgery + Ongoing medical therapy (Steroids, nasal douches) + Immunotherapy? + Antifungal drugs?	Surgical debridement + Systemic antifungals + Immune reconstitution
Prognosis	Excellent cure rate	Chronic, but fairly good control of disease is achievable by means of surgery(ies) and ongoing medical therapy +/- immunotherapy +/- Antifungal drugs	High mortality rate, mostly related to absence of host immune reconstitution and the extent of involvement on recognition of the disease

AFRS: allergic fungal rhinosinusitis, AIFRS: acute invasive fungal rhinosinusitis. Modified from Callejas CA, Douglas RG. Fungal rhinosinusitis: what every allergist should know, Clin Exp Allergy, 2013;68:835-849, with permission from Wiley-Blackwell.)

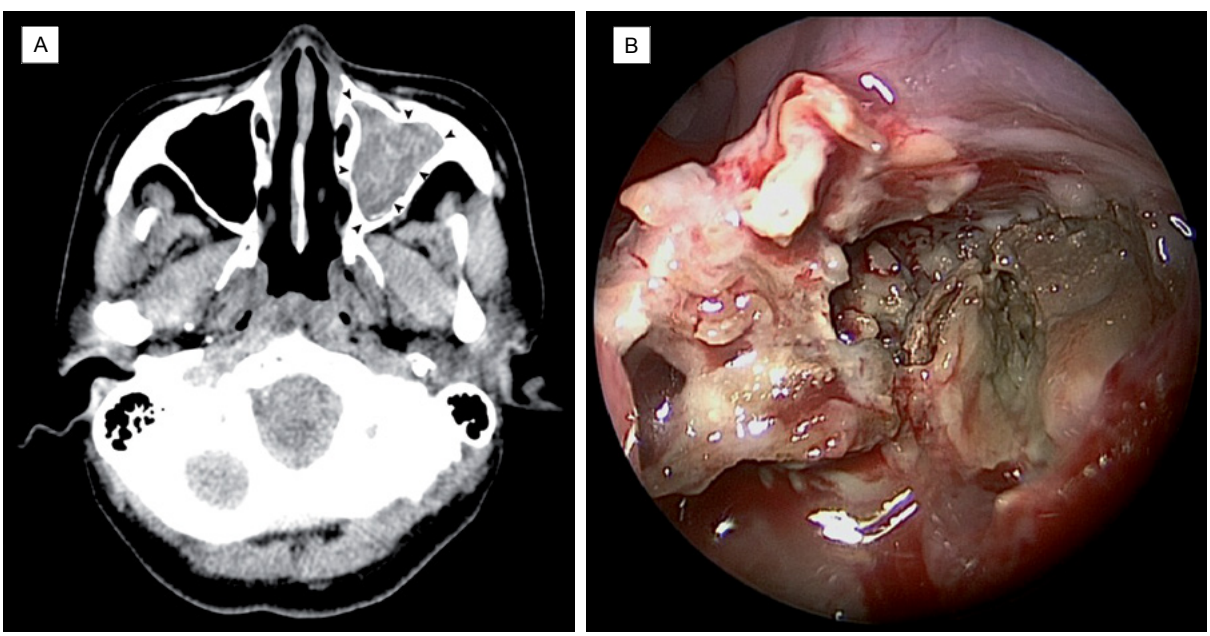

Figure 1 A. An axial CT scan demonstrating a fungal ball in the left maxillary sinus (black arrowheads). Note the heterogeneous radiodensity that is characteristic of this condition. Frequently, discrete and very dense areas (even metallic densities) are seen due to local calcification in the centre of the hyphae masses. B. An intra-operative photograph of the same patient. Thick fungal debris is being removed through a middle meatal antrostomy. (*Modified from Callejas CA, Douglas RG. Fungal rhinosinusitis: what every allergist should know, Clin Exp Allergy, 2013;68:835-849, with permission from Wiley-Blackwell.*)

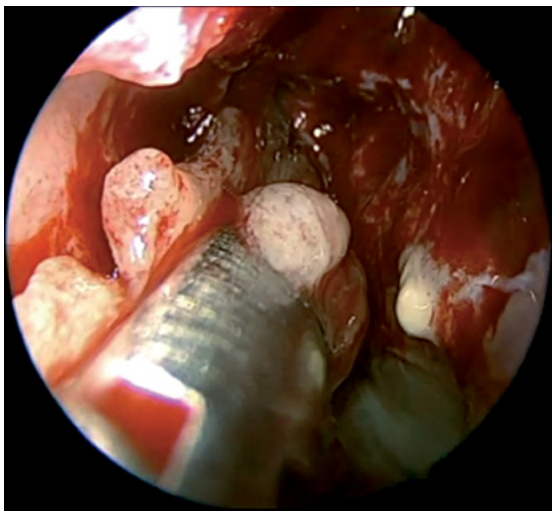

Figure 2 Eosinophilic mucin being extracted from the sphenoid sinus with a grasping forceps. The thick and tenacious consistency can be appreciated.

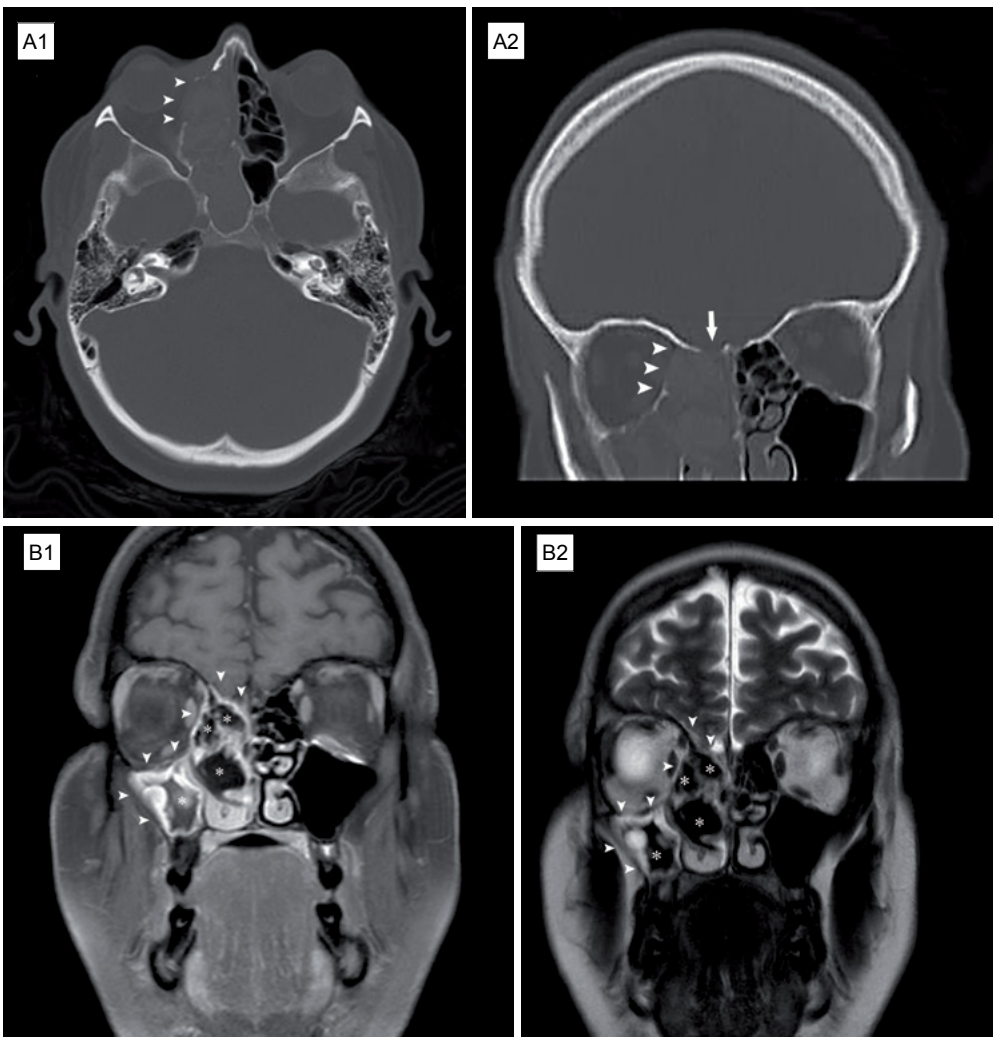

Figure 3 A. Sinus CT scans of a patient with allergic fungal rhinosinusitis (AFRS): 1. Medial orbital wall thinned and expaned laterally by the ethmoid sinus content (arrowheads), 2. Erosion of the skull base (arrow) and lateral expansion of the thinned medial orbital wall (arrowheads). B. MRI of the same patient:1. T1-weighted image showing central hypointensity (asterisks) and peripheral enhancement of right side sinuses (arrowheads), 2. T2-weighted image showing central void signal (asterisks) and peripheral enhancement of right side sinuses (arrowheads). (*Reproduced with permission from Callejas CA, Douglas RG. Fungal rhinosinusitis: what every allergist should know, Clin Exp Allergy, 2013;68:835-849, with permission from Wiley-Blackwell.*)

TABLE 2

Bent and Kuhn diagnostic criteria for allergic fungal rhinosinusitis
1) Nasal polyposis
2) Presence of fungi on direct microscopy or culture of sinus content
3) Eosinophilic mucin without fungal invasion into sinus tissue
4) Type I hypersensitivity to fungi demonstrated by skin testing or *in vitro* testing
5) Characteristic computed tomographic findings, including sinus expansion or heterogeneous opacification

Figure 4 Left orbital exenteration in a patient with acute invasive fungal rhinosinusitis.

teria for diagnosis of AFRS are still widely accepted (Table 2). However, identical clinical forms of CRS, but without type I hypersensitivity to fungi (eosinophilic fungal rhinosinusitis) or without proven presence of fungi (eosinophilic mucin rhinosinusitis) have been described, raising the question whether AFRS as defined by the Bent and Kuhn criteria represents just a subset of this condition. The treatment of AFRS is predominantly surgical and involves the removal of all fungal debris and associated NP. Postoperative topical medical therapy with saline lavage and intranasal corticosteroids probably increases the chance of achieving a good long-term outcome. In spite of these measures, some patients will need multiple surgeries to achieve control of their disease. Antifungal drugs and immunotherapy may have a role as adjuvant therapy, but no clinical trial has demonstrated convincing efficacy.

INVASIVE DISEASE

Acute invasive fungal rhinosinusitis (AIFRS) is an acute life-threatening condition, in which the fungal infection invades underlying mucosal tissue, as a result of an impaired immune response. It tends to spread aggressively, and often has a fulminant course, progressing over hours. Eye, brain, palate and skin involvement can occur (Figure 4). The symptoms are often non-specific and a high index of suspicion in an immunocompromised patient with sinonasal symptoms and/or fever is mandatory to facilitate early diagnosis. Treatment of AIFS has three pillars: (1) urgent surgical debridement of all the necrotic tissue, (2) immediate initiation of systemic antifungal therapy and (3) immune reconstitution (if possible). AIFS is still associated with high mortality rates (10% to 50%) determined mainly by the potential for host immune reconstitution and the extent of involvement at the time of recognition of the disease.

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17 CO-MORBIDITIES OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Chronic rhinosinusitis (CRS) with/without nasal polyposis (NP) and asthma are diseases that often occur together
- Allergic rhinitis is a common coexisting disease in patients with CRS
- Sinonasal inflammation is found in most cystic fibrosis (CF) patients
- The number of cases with a concomitant diagnosis of sinusitis is significantly higher in the children with gastro-esophageal reflux disease (GERD)

Chronic rhinosinusitis (CRS) with and without nasal polyps (NP) (Figure 1) represent different stages of one chronic inflammatory disease of the mucosa of the nasal cavity and paranasal sinuses. Co-existence of CRS with NP and asthma and rather similar characteristics of inflammation support assumption that all are, at least in part, the same disease process. Nasal allergy is also related to inflammatory chronic sinusitis as a risk factor. There are a lot of co-morbidities which often occur with CRS (Table 1).

CRS AND ASTHMA: CRS with/without NP and asthma are diseases that often occur together. A recent large-scale European survey confirmed the strong association between CRS and asthma. CRS in the absence of nasal allergies was associated with late-onset asthma.

Figure 1 Endoscopic view of nasal polyps.

CRS AND ALLERGIC RHINITIS: Allergic rhinitis is a common coexisting disease in patients with CRS. The data about the association between the 2 diseases in children is variable. In a series of 42 patients with CRS refractory to medical treatment in which a RAST test as well as a CT scan was available, 40% of the patients were atopic and 60% were non-atopic.

CRS AND CYSTIC FIBROSIS: Rhinosinusitis may often be a presenting symptom of the so-called atypical cystic fibrosis (CF) pa-

TABLE 1

Co-morbidities of chronic rhinosinusitis
Asthma
Allergic rhinitis
Cystic fibrosis
Chronic Obstructive pulmonary disease
Aspirin Exacerbate Respiratory Disease
Immunodeficiency
Hypertrophied adenoids
Gastro-esophageal Reflux Disease
Primary Ciliary Dyskinesia

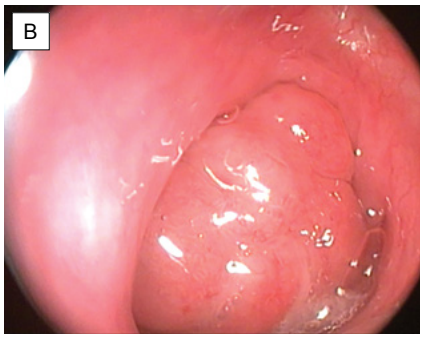

Figure 2 Endoscopic view of hypertrophied adenoids. Partial (A) and total (B) obstruction of choana by hypertrophied adenoids is shown.

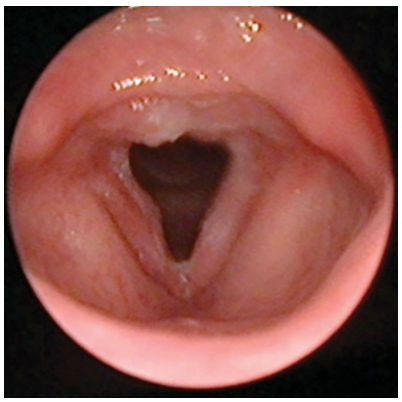

Figure 3 Laryngeal findings of gastroesophageal reflux disease (GERD). Oedema, erythema, and hyperkeratosis were shown in the interarytenoid region.

tients, with normal or borderline sweat test result and carrying only one mild mutation of the CFTR gene. Sinonasal inflammation is found in most CF patients, with NP being present in 1/3 of CF patients.

CRS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A majority of chronic obstructive pulmonary disease (COPD) patients presenting at an academic unit of respiratory disease report sinonasal symptoms. Several pro-inflammatory mediators have been found increased in the nasal lavages of COPD patients. The presence of nasal symptoms is associated with the overall impairment of the quality of life in COPD.

CRS AND ASPIRIN EXACERBATED RESPIRATORY DISEASE: The presence of hypersensitivity to aspirin or other NSAIDs in a patient with rhinosinusitis and NP is associated with a particularly persistent and treatment-resistant form of the disease, coexisting usually with severe asthma and referred to as the "aspirin triad".

CRS AND IMMUNODEFICIENCIES: There was an association between rhinosinusitis and primary immunodeficiencies. Among CRS patients, who are referred for immune evaluation, up to half may have T lymphocyte dysfunction, while roughly 20% have decreased IgG, IgA or IgM. In addition, nearly 10% have common variable immune deficiency (CVID).

CRS AND HYPERTROPHIC ADENOIDS IN CHILDREN: Nasal discharge could be due to adenoiditis alone and that the bacterial reservoir of the adenoids more than their size was important in the relationship between CRS and the hypertrophied adenoids (Figure 2).

GASTROESOPHAGEAL REFLUX DISEASE: The number of cases with a concomitant diagnosis of sinusitis was significantly higher in the children with gastro-esophageal reflux disease (GERD) (4.19%) compared to the control group (1.35%) (Figure 3).

PRIMARY CILIARY DYSKINESIA: Primary ciliary dyskinesia (PCD) is the most common cause of ciliary dysfunction. PCD is an autosomal recessive disorder present in 1 of 15,000 of the population. Half the children with PCD also have situs inversus, bronchiectasis, and CRS and are known as Kartagener's syndrome. The diagnosis should be suspected in a child with atypical asthma, bronchiectasis, chronic wet cough and mucus production, rhinosinusitis, chronic and severe otitis media (especially with chronic drainage in children with ear tubes).

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18 UNCONTROLLED RHINOSINUSITIS

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KEY MESSAGES

- A significant percentage of chronic rhinosinusitis (CRS) patients are uncontrolled
- A wide variety of factors can contribute to poor disease control
- Assessment of disease control should guide alterations in therapy in CRS

In general, the goal of treatment for any medical condition is to achieve and maintain clinical control. In contrast to asthma, the concept of control of disease has only recently been introduced in the field of allergic rhinitis (AR) and chronic rhinosinusitis (CRS). In asthma treatment guidelines are based on the assessment of control.

A number of terms have been used in the past to describe uncontrolled disease. Bousquet et al. suggested the term SCUAD (severe chronic upper airway disease) to define those patients whose symptoms are inadequately controlled despite adequate (ie, effective, safe, and acceptable) treatment based on guidelines. The patients have impaired quality of life, social functioning, sleep, and school/work performance. SCUAD patients can have several phenotypes like severe uncontrolled AR, non-allergic rhinitis, or CRS with or without nasal polyps (NP). Other terms that can be found in the literature are recalcitrant rhinosinusitis, treatment-recalcitrant rhinosinusitis, refractory rhinosinusitis, and difficult to treat rhinosinusitis.

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) defined in 2012 EPOS criteria for difficult to treat and disease control in CRS. Disease control in CRS was defined a disease state in which the patients do not have symptoms or the symptoms are not bothersome, if possible combined with a healthy or almost healthy mucosa and only the need for local medication. Patients who do not reach an acceptable level of control, despite adequate surgery, intranasal corticosteroid treatment and up to 2 short courses of antibiotics or systemic corticosteroids in the last year can be considered to have difficult-to-treat rhinosinusitis. In EPOS 2012 a method of evaluating control was proposed (Table 1). Recently a modification of the EPOS 2012 control method was proposed: the "NOSE" staging system measuring only nasal obstruction, systemic medication use, and endoscopic signs of inflammation.

It has been estimated that up to 20% of CRS patients are not well controlled despite receiving combination maximal medical therapy and endoscopic sinus surgery. A wide variety of factors can contribute to poor disease control, including patient-related factors such as eosinophilic CRS, osteitis, biofilms, other underlying diseases like cystic fibrosis and vasculitis and physician-related factors such as inappropriate sinus surgery or inaccessible topical therapy. Periodical assessment of disease control should guide alterations in therapy according to a stepwise approach and optimize CRS management. A stepwise approach based on the EPOS2012 guidelines is suggested in Figure 1.

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TABLE 1

Assessment of current clinical control of CRS*

Characteristic	Controlled (all of the following)	Partly Controlled (at least one present)	Uncontrolled
Nasal blockage	Not present or not bothersome	Present on most days of the week	Three or more features of partly controlled CRS
Rhinorrhea/ Postnasal drip	Little and mucous	Mucopurulent on most days of the week	
Facial pain/headachec	Not present or not bothersome	Present	
Smell	Normal or only slightly impaired	Impaired	
Sleep disturbance or fatigue	Not impaired	Impaired	
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa (nasal pol-yps, mucopurulent secretions, inflamed mucosa)	
Systemic medication needed to control disease	Not needed	Need of a course of antibiotics or systemic corticosteroids in the last three months	Need of long term antibiotics or systemic corticosteroids in the last month

**Data from Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012:1-298.*

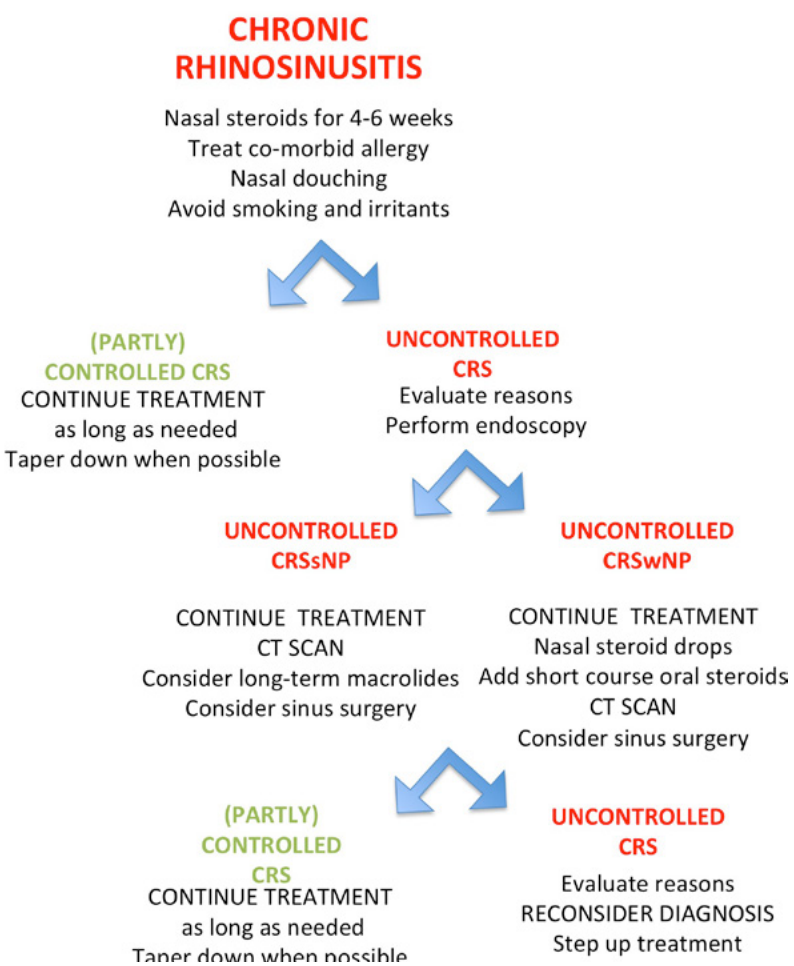

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Figure 1 Treatment of CRS based on control. (*Reproduced with permission from Hellings PW, Fokkens WJ, Akdis C, et al. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? Allergy 2013;68:1-7, with permission from Willey Blackwell.*)

19 THE GLOBAL BURDEN OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Symptoms of chronic rhinosinusitis are reported by about 10% of the population, but there is considerable variation
- About 5% of the population report that they have been given a diagnosis of CRS
- CRS is associated with smoking and with late onset asthma, but not with early onset asthma
- People with CRS and people with asthma have an approximately equivalent detriment in their quality of life

Chronic rhinosinusitis (CRS) is a condition that has been largely ignored by epidemiologists. It is diagnosed by a combination of symptoms and further confirmatory tests using either endoscopy or computed tomography. In epidemiological surveys reliance is generally placed on symptom questionnaires and occasionally on reported diagnoses; confirmatory tests are generally not feasible. Questionnaires based on international diagnostic guidelines are not adequate to make a clinical diagnosis but have had some validation as indicators of disease.

Studies of CRS in adults have given estimates of prevalence of around 8-10% but there is some variation, some of which is related to differences in the way the condition is assessed. A multi-site survey in Europe (Figure 1) based on symptom questionnaires gave estimates between 6.9 and 21.7% and a similar multisite study in China gave prevalences between 4.8 and 9.7%. In general, prevalences based on self-reported diagnoses give figures about a half of these figures, but studies in north America have given estimates of 11% for sinusitis in the USA and 6.7% for rhinosinusitis in Canada based on self-reported diagnoses.

The European studies suggest that CRS is more common in older age groups, though elsewhere the peak prevalence in is early adulthood. This difference may represent differences in disease between birth cohorts as well as differences in susceptibility as people age. Most studies agree that smoking is strongly associated with disease (Figure 2). CRS is, in turn, a risk factor for late onset asthma, though it is not associated with early onset asthma. In this respect, it is different from allergic rhinitis (Figure 3).

Studies using generic measures of quality of life suggest that the impairment of QOL is similar in magnitude for patients with asthma and patients with CRS (Figure 4). Those who have both conditions have a worse quality of life than those who just have one condition.

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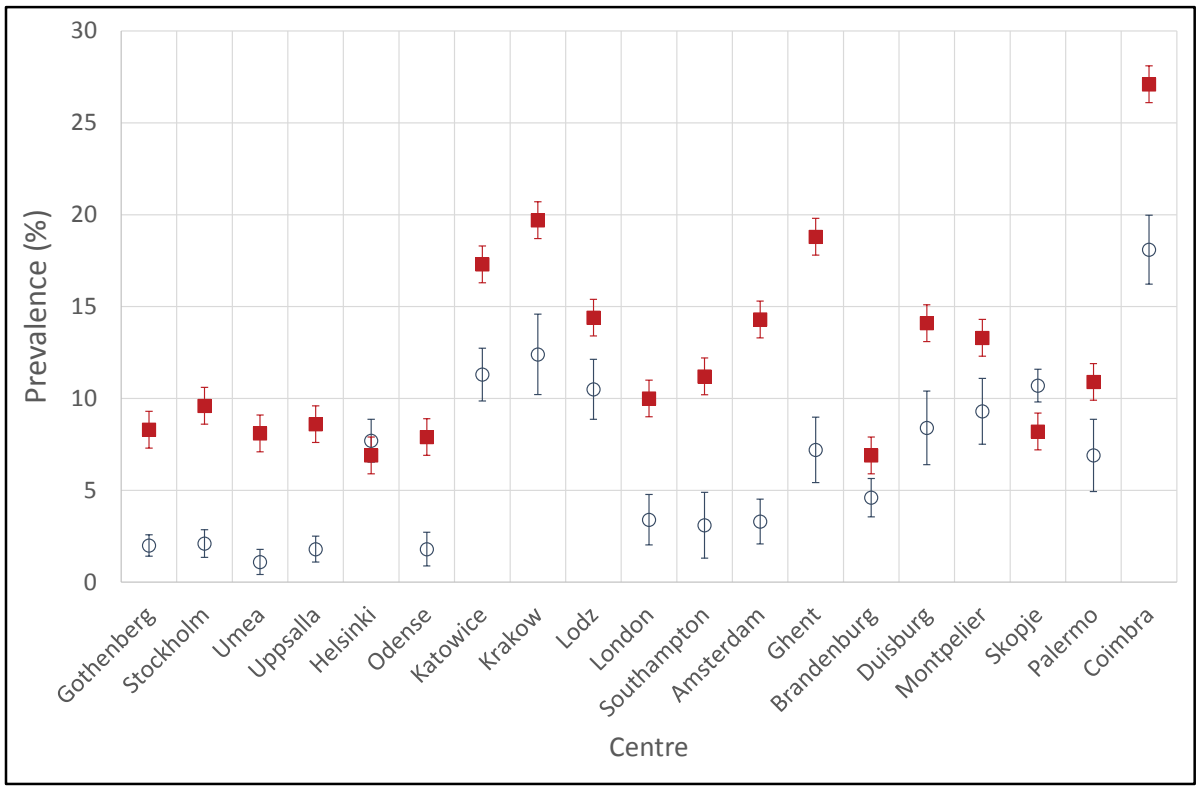

Figure 1 Prevalence (%) of symptoms of chronic rhinosinusitis and of a self-reported diagnosis of CRS in 17-70 year old populations across Europe. (*Redrawn from Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA2LEN study. Allergy 2011;66:1216-1223.*)

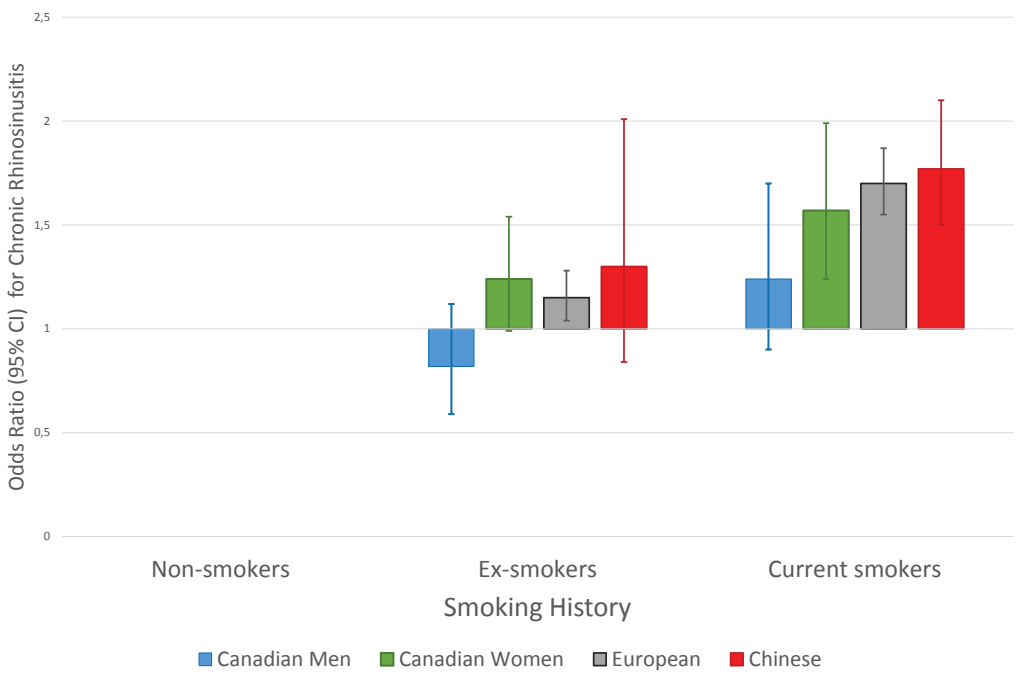

Figure 2 Association of chronic rhinosinusits with smoking status (odds ratio and 95% confidence interval) in three surveys in Canada (ref 5) Europe (ref 2) and China (ref 3)

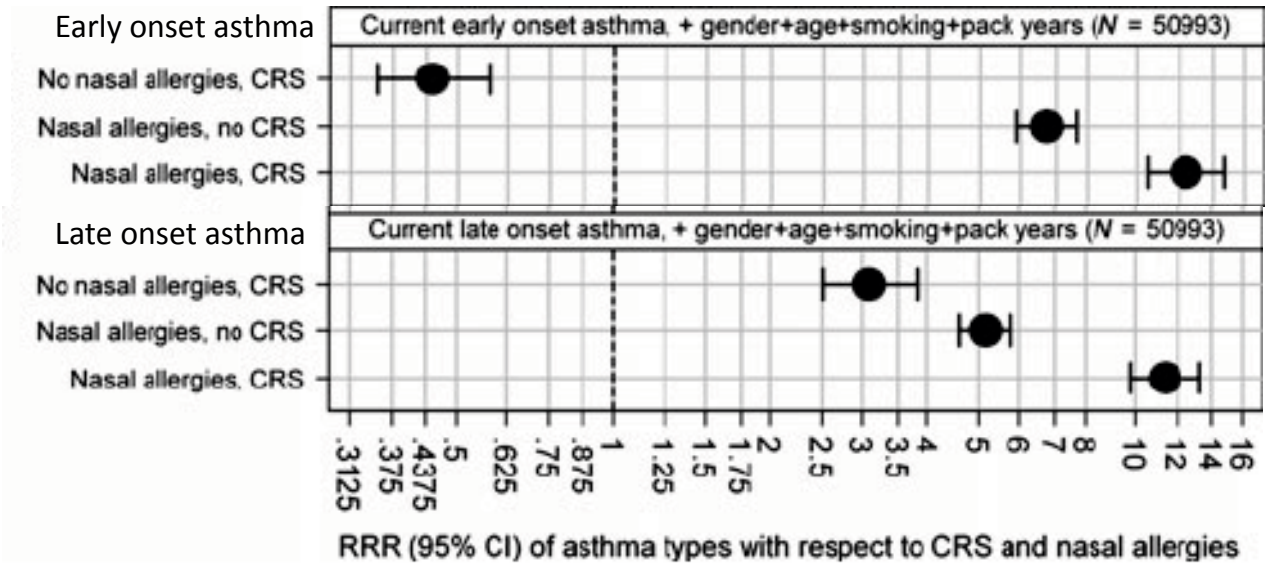

Figure 3 Risk of early and late onset asthma by upper airway disease (Adjusted relative risk ratio compared with participants with no nasal allergies and no chronic rhino-sinusitis) (*Adapted from Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: The GA2LEN survey in Europe. Allergy 2012;67:91-98.*)

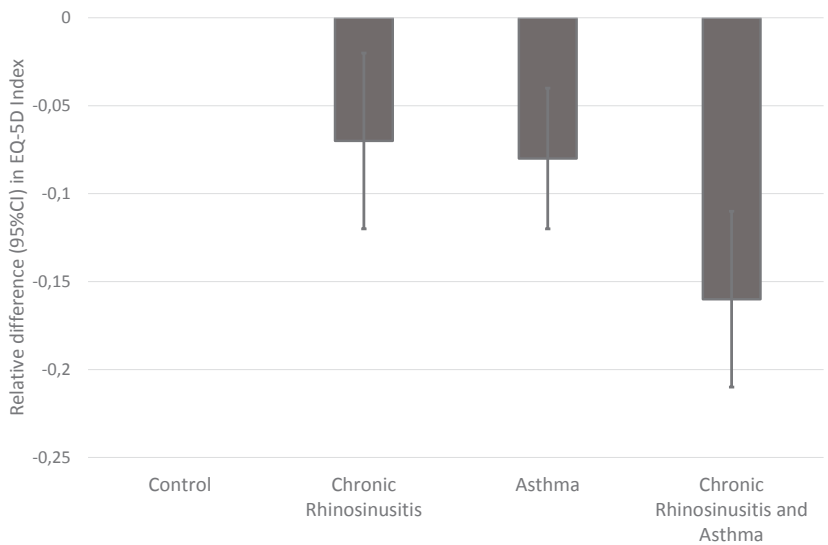

Figure 4 Relative reductions in quality of life [EQ-5D] in those with chronic rhinusitis, asthma or both conditions, compared with those with none of these conditions. (*Drawn from data in Ek A, Middleveld R, Bertilsson H, et al. Chronic rhinosinusitis in asthma is a negative predictor of quality of life: results from the Swedish GA2LEN survey. Allergy 2013;68:1314-1321.*)

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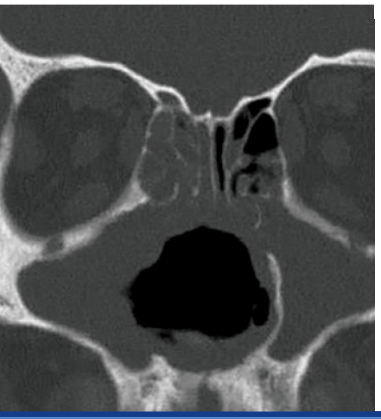
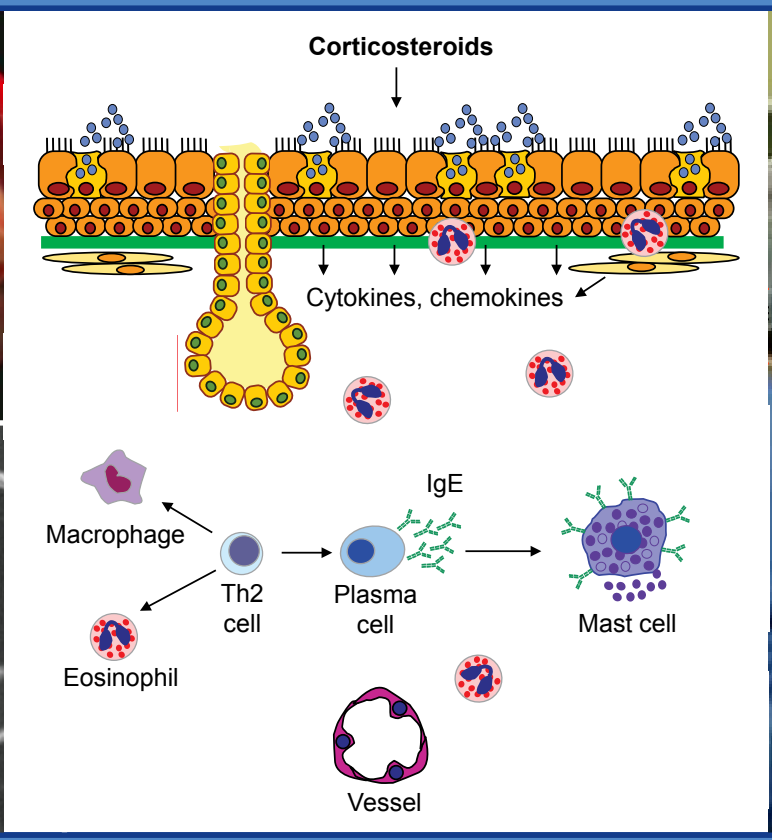
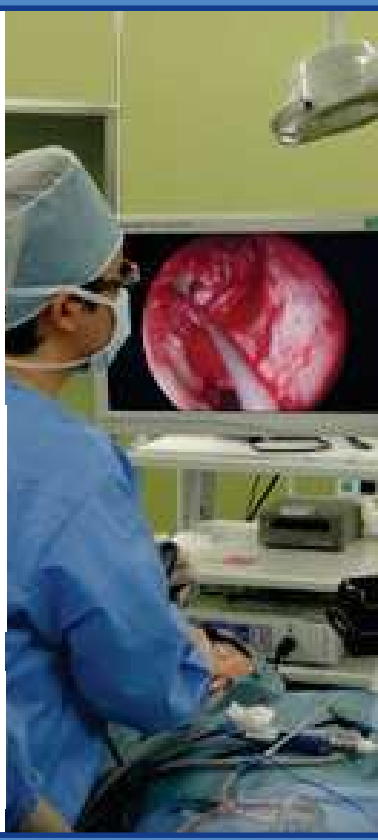
Section H







CHRONIC RHINOSINUSITIS - DIAGNOSIS AND MANAGEMENT

* Nasal endoscopy
* Imaging of the paranasal sinuses in chronic rhinosinusitis
* Smell testing in chronic rhinosinusitis
* Medical management of chronic rhinosinusitis
* Topical and systemic corticosteroids in chronic rhinosinusitis
* Long-term use of antibiotics in chronic rhinosinusitis
* Immune modulation in chronic rhinosinusitis
* Evidence – based surgery in chronic rhinosinusitis
* Surgery for chronic rhinosinusitis with nasal polyps
* Interfacing medical and surgical management of chronic rhinosinusitis
* The challenges of chronic rhinosinusitis management

1 NASAL ENDOSCOPY

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KEY MESSAGES

- Nasal endoscopy identifies accessible pathologic changes in the sino-nasal mucosa with greater precision than imaging and permits accurate evaluation of the efficacy of medical therapy in chronic rhinosinusitis (CRS)
- In addition the method allows endoscopically directed cultures and/or biopsies
- Nasal endoscopy is essential to identify persistent inflammation following sinus surgery and hence guide appropriate therapy

Nasal endoscopy is an essential element of rhinologic examination of chronic sinonasal complaints. It has been well documented that symptoms of chronic rhinosinusitis (CRS) do not correlate well with CT findings, and that the sensation of nasal obstruction does not correlate well with nasal airflow alone.

Performed under topical anesthesia and typically following decongestion, it provides for a detailed examination of the nose, nasopharynx, middle meatus and spheno-ethmoidal recess. A 2.7mm or 4mm 30º or 45º endoscope is utilized most commonly, although a 70º endoscope may be required in some situations. As an alternative, flexible fiberoptic endoscopy can provide good visualization, but does not facilitate endoscopically directed culture or biopsy.

Following the application of a topical xylocaine or tetracaine spray, usually combined with a topical decongestant (oxymetazaline), nasal endoscopy is best performed in a systematic fashion with three passes (below the inferior turbinate, between the inferior and middle turbinate and, when possible, with direct examination of the middle meatus. For the latter, additional anesthesia (such as with 4% cocaine on nasal applicators) may be required.

The first pass of the endoscope provides an overview of the nasal anatomy, of the Hausner's valve, the evaluation of the status of the inferior turbinate and the nasopharyngeal anatomy. Passing the endoscope between the inferior and middle turbinate allows visualization of the uncinate process and anterior middle meatus, sphenoethmoidal recess and some visualization of the olfactory cleft (Figure 1). The middle meatus is often best entered inferiorly, thereby permitting visualization of the ethmoidal bulla, and hiatus semilunaris. Gentle pressure on the uncinate process may reveal edema within the ethmoidal infundibulum, frequently the initial area involved in inflammatory disease (Table 1).

Careful evaluation should be performed for the presence of polyps, edema, drainage throughout the examination (Figure 2). Endoscopically directed culture is performed when indicated, and biopsy of suspicious lesions can be performed under local anesthesia when indicated. For endoscopic biopsy, a 5cm 27G needle may be bent appropriately, and when attached to a 1cc syringe usually allows direct injection of the majority lesions within the nose. Biopsy of possible juvenile angiofibroma lesions should be avoided, and careful consideration should be given prior to office biopsy of other vascular lesions.

Postoperatively, nasal endoscopy directs the duration and types of medical therapy, as well as the necessity for debridement. Following

TABLE 1

Nasal endoscopy steps and what can be visualised		
1st pass	Along floor of the nose	Inferior turbinate Hausner's valve Inferior meatal window Posterior Choana Nasopharynx Eustachian tube
2nd pass	Between middle and inferior turbinate	Anterior middle meatus Uncinate process Inferior middle meatus Accessory ostia Sphenoethmoidal recess Superior turbinate Sphenoid ostium
3rd pass	Middle meatus	Hiatus semilunaris Infundibular edema Bulla Frontal recess openings

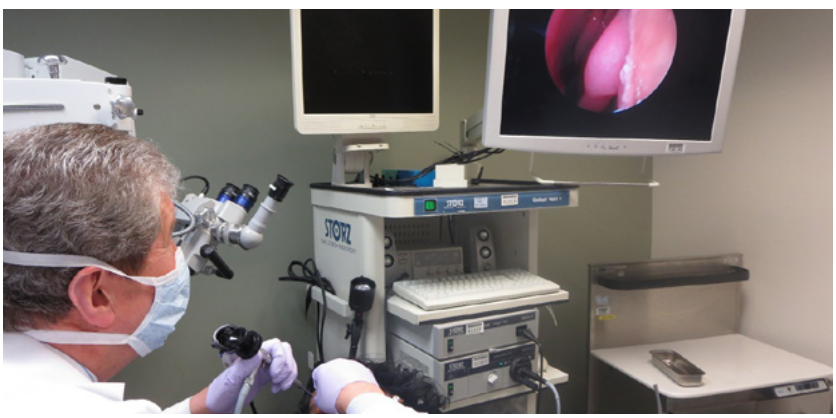

Figure 1 Outpatient nasal endoscopy. The procedure is performed under local anesthesia with the patient seated or lying supine in an examination chair. A 30º endoscope is usually chosen for the initial evaluation. The image on the monitor shows the left inferior and middle turbinate.

a complete endoscopic surgical procedure, it should be possible to visualize all the sinuses with appropriately angled telescopes. In patients with persistent or recurrent disease, particular attention should be directed to the frontal recess and to the natural ostium of the maxillary sinus. Ensuring the natural ostium of maxillary sinus is truly open and not scarred anteriorly frequently requires utilization of a 45º or 70º endoscope.

Thus nasal endoscopy complements the careful patient history in the diagnosis of CRS, augments the information which can be obtained by imaging and provides objective evidence of the therapeutic response over time, especially in postoperative patients who are frequently essentially asymptomatic despite persistent inflammatory disease.

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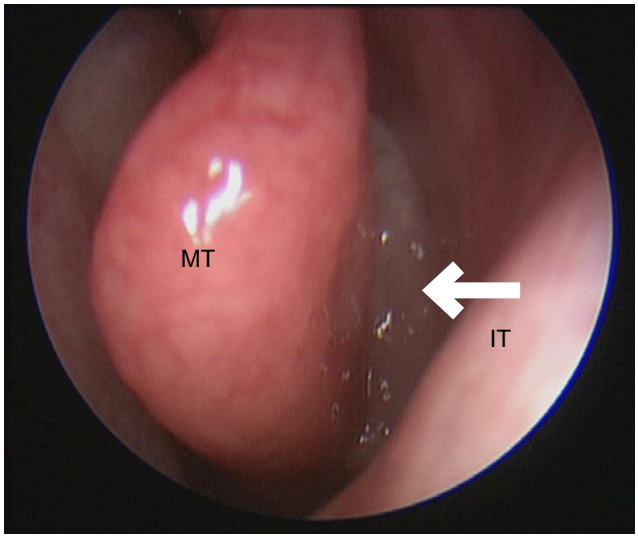

Figure 2 Nasal endoscopic examination of the left nasal cavity of a patient with chronic rhinosinusitis with a 30º endoscope demonstrates polypoid mucosa within the middle meatus (arrow). MT= middle turbinate, IT= Inferior turbinate

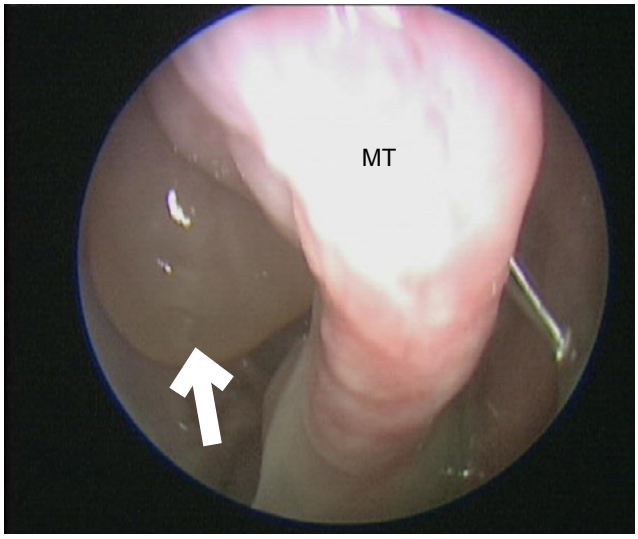

Figure 3 Nasal endoscopy of the right middle meatus with 30º endoscope in a patient with aspirin exacerbated respiratory disease (AERD) and prior surgery demonstrates a large polyp in the right ethmoid cavity (arrow). MT= Middle meatus

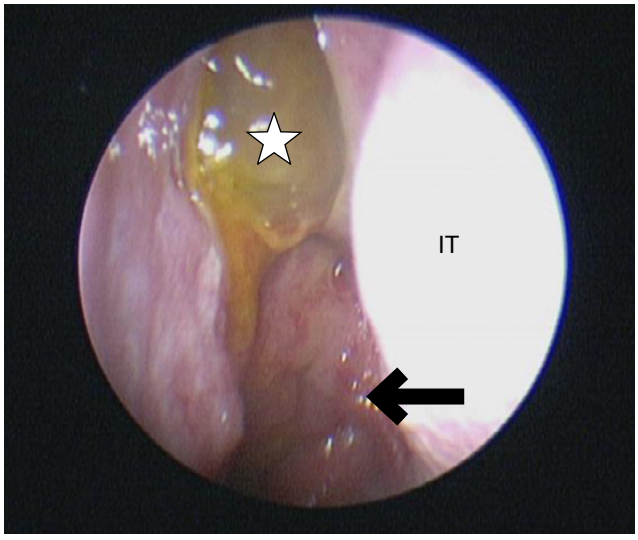

Figure 4 Nasal Endoscopy of the left nasal cavity with a 30º telescope in a patient with a large nasopharyngeal tumor demonstrates the nasopharyngeal mass (arrow) and polypoid mucosa within the sphenoethmoid recess (star). It is important to note that the wide angle of view of nasal endoscopes makes extramucosal masses perpendicular to the endoscope more difficult to identify. IT= Inferior turbinate).

2 IMAGING OF THE PARANASAL SINUSES IN CHRONIC RHINOSINUSITIS

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Computed tomography (CT) is the most commonly used imaging modality for evaluation of inflammatory sinus mucosal disease. CT allows optimal evaluation of the bony anatomy of the paranasal sinuses, the drainage pathways, as well as the mucosal disease (Figure 1). Volumetric scanning with a multi-detector CT scan, use of 0.5 mm or 0.6 mm axial acquired CT images, and reformatted images in the axial, coronal, and sagittal planes afford an excellent display of the regional soft tissue and bone detail.

Chronic rhinosinusitis (CRS) is a clinical diagnosis made in the setting of persistent sinus symptoms for greater than 12 consecutive weeks, and is the most common indication for sinus imaging. CT is an excellent complementary tool in displaying the extent of inflammatory disease beyond what is available with clinical inspection, anterior rhinoscopy and nasal endoscopy. Sinusitis often results from an obstruction of the drainage pathways of the sinuses, the ostiomeatal pathways. Obstruction of the frontal recess, middle meatus and maxillary infundibulum as well as the sphenoethmoid recess and sphenoid sinus ostium

KEY MESSAGES

- Computed tomography (CT) is the most commonly used imaging modality for evaluation of inflammatory sinus mucosal disease
- CT allows optimal evaluation of the bony anatomy of the paranasal sinuses, the drainage pathways, as well as the mucosal disease
- CT is an excellent complementary tool in displaying the extent of inflammatory disease beyond what is available with anterior rhinoscopy and nasal endoscopy
- Magnetic resonance imaging (MRI) provides better soft tissue resolution and is useful in certain instances including complications of sinusitis and in differentiating inflammatory mucosal disease from neoplasia

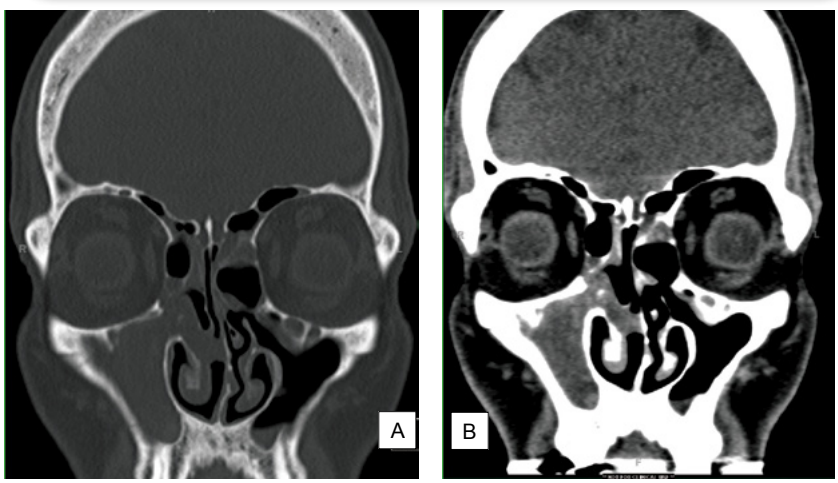

Figure 1 Coronal images of the paranasal sinuses through the region of the ostiomeatal units in bone (A) and soft tissue (B) windows. There is polyp in the right middle meatus with mucosal disease in the right maxillary sinus, with minimally hyper attenuating secretions within.

Figure 2 Coronal image in bone window images shows sclerotic osteitic thickening of the sphenoid sinus walls with chronic moderate sinus mucosal disease and punctate calcifications. Incidentally noted is an Onodi cell on the left superior to the left sphenoid sinus lumen.

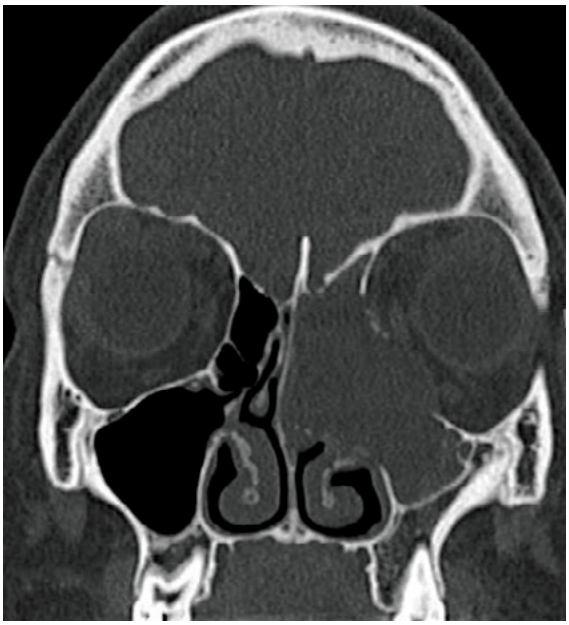

Figure 3 Coronal bone window image demonstrating a large left ethmoid mucocele obstructing and partially occupying the left maxillary antrum. There is focal osseous disruption of the inferior portion of the lamina papyracea and bulging of the mucocele into the orbit.

will block the mucociliary drainage and air exchange within the sinuses resulting in an inflammatory process.

The secretions opacifying the sinus lumen have a variable appearance. In the acute phase, the low viscosity secretions are of intermediate to low attenuation on CT (10-25 Hounsfield units). There is a uniform mucosal thickening along the sinus walls accompanied by a fluid exudate that may result in an air-fluid level within the sinus. If the obstruction continues, the mucosal thickening will increase and may proceed to totally occupy the obstructed sinus. With chronicity, the secretions become more viscous with increased CT densities (30-60 HU), resulting from the relative increase in the protein concentration as the water component decreases. These changes are not always visually apparent, and therefore a distinction between acute,subacute and chronic inflammation inflammation cannot always be made on CT scans. With time, however, the inflammation may extend into the bony perimeter of the sinus, with sclerosis and thickening of the sinus walls representing osteitis, and a sign of chronicity (Figure 2).

Magnetic resonance imaging (MRI) provides better soft tissue resolution and is useful in certain instances including complications of sinusitis and in differentiating inflammatory mucosal disease from neoplasia. On MRI, the chronic proteinaceous or inspissated secretions appear hyperintense on the T1-weighted images and hypointense on the T2-weighted images with peripheral rim of mucosal enhancement on the post contrast images. It is also useful to remember that the viscous secretions may restrict diffusion in the absence of frank purulent change.

In general, CRS is not associated with bone erosion. Should bone erosion be present, one needs to consider the presence of other pathologies such as a mucocele, invasive fungal sinusitis, granulomatosis with polyangiitis, or a superimposing neoplasm. Should the bone erosion affect the skull base the possibility of a mucocele, meningocele, meningoencephalocele, or a neoplasm should be considered. Nasal septal destruction can also occur with rhinosinusitis due to cocaine use, lymphoma, and post unsuccessful septoplasty. To reach a more focused diagnosis, MRI with and without intravenous gadolinium based contrast administration will be very helpful. Mucocele (Figure 3) is a complication of CRS resulting from a persistent

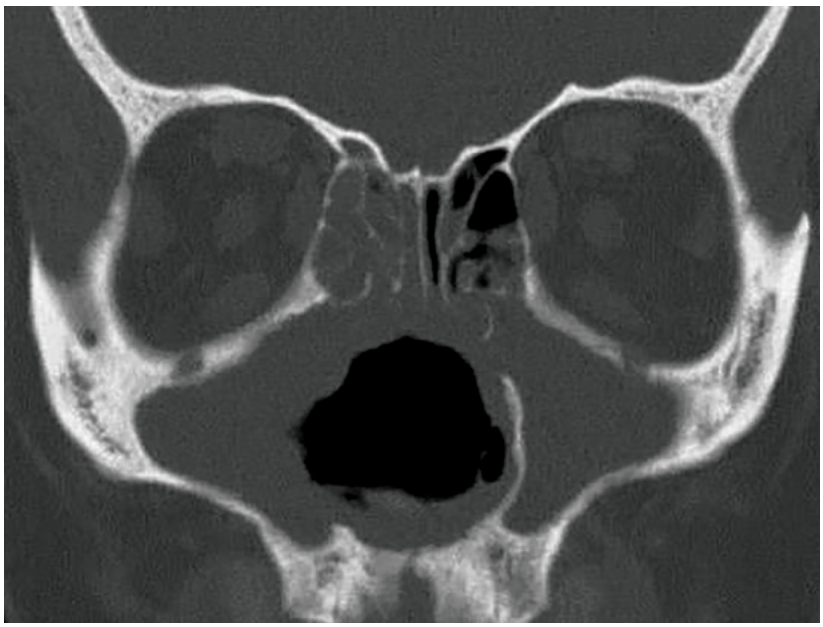

Figure 4 Coronal bone window image demonstrating near complete opacification of the paranasal sinuses in a patient with Granulomatosis with polyangiitis (GPA). There is destruction of the medial right maxillary wall, the turbinated bilaterally and the nasal septum.

obstruction of drainage pathway with subsequent expansion of the sinus lumen, and may be associated with bony erosion. These most commonly involve the ethmoid and frontal sinuses, although maxillary and sphenoid sinuses may also be affected. Secondary infection of a mucocele may result in a mucopyocele. Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis is a systemic necrotizing vasculitic syndrome that involves the sinonasal structures with mucosal thickening, osteitis, bony erosion, and extension into the orbits, and rarely the intracranial compartment. Bone destruction may involve the medial maxillary walls, lamina papyracea, with nasal septal destruction being a characteristic feature (Figure 4)

Punctate calcific densities within inspissated proteinaceous secretions may be occasionally be visible on CT scans, and represent fungal concretions related to a superimposed fungal colonization without a frankly invasive fungal sinusitis. Noninvasive fungal colonization occurs in the CRS or in conjunction with polyposis. The presence of trace metallic elements in the fungal filaments occasionally will result in a profoundly hypointense signal on T2 weighted images mimicking an aerated sinus.

Retention cysts are often seen as well-defined lesions within the sinuses, most commonly in the maxillary sinuses. These are usually incidental findings on imaging studies although large cysts may interfere with the drainage pathways. These may also demonstrate slightly increased protein content and related signal changes on MRI.

Antrochoanal and sphenochoanal polyps appear as well-defined masses that arise from the maxillary antrum or the sphenoid sinus respectively. The antrochoanal polyp extends through the accessory maxillary ostium into the middle meatus, extending through the posterior choana and presenting as a nasopharyngeal mass.

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3 SMELL TESTING IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Psychophysical olfactory testing reveals that patients with chronic rhinosinusitis (CRS) have impaired olfactory function, mainly those with nasal polyps (CSRwNP)
- Orthonasal and retronasal olfactory function may be explored for diagnostic purposes and give important guidance in the management of the CRS patients
- Chemosensory event related potentials are considered a more objective method for olfactory function
- CT scan of the paranasal sinuses confirms the diagnosis of CRS and magnetic resonance imaging may reveal olfactory bulb volume variations

Olfactory dysfunction is one of the symptoms included in the diagnostic criteria for chronic rhinosinusitis (CRS) with or without nasal polyposis (CRSsNP or CRSwNP), underlining the importance of this specific symptom in patients with sino-nasal disease. Even if olfactory impairment is a common symptom affecting 61-83% of patients with CRS, up to one quarter of the patients with CRS are unaware of their olfactory dysfunction.

Psychophysical tests results show that patients with CRSsNP or CRSwNP have quantitative disorders (hyposmia more frequently then anosmia), report fluctuating symptoms and have fewer qualitative disorders such as parosmia (28%) and phantosmia (7%) than patients without sino-nasal aetiology of smell pertubation. Also, it is widely accepted that patients with CRSwNP have lower olfactory function than patients with CRSsNP (Figure 1). Psychophysical testing is important when medical and/or surgical treatments are not effective or when the dysfunction of the chemosensory perception is important for the patient (Figure 2).

Olfactory dysfunction in CRS is caused by swollen or hypertrophic nasal mucosa or nasal polyps, inducing an impaired access of odorants to the olfactory cleft. However there is only little correlation between nasal resistance and the degree of olfactory dysfunction. In addition, surgical therapy, although improving the nasal patency, has sometimes uncertain results when considering the olfactory recovery. Biopsies of the olfactory nasal neuroepithelium in patients suffering from CRS revealed inflammatory changes in the nasal mucosa and apoptotic pathological changes, including the olfactory receptor neurons and olfactory supporting cells. Infiltrating inflammatory cells release inflammatory mediators, which are known to trigger hypersecretion in respiratory and Bowman's glands altering the ion concentrations of olfactory mucus and affecting the olfactory transduction process. In addition, cytokines and mediators, particularly those released by eosinophils, may be toxic to olfactory receptor neurons and the degree of inflammation changes in the neuropithelium is related to the severity of olfactory dysfunction.

Evaluation of the orthonasal function can be performed through many standardized tests. The Sniffin' Sticks test and the University of Pennsylvania smell identification test (UPSIT) are the most frequently used (Figure 3). These

Figure 1 Endoscopic examination; A: CRSsNP; B: secretions in the right olfactory cleft; C: CRSwNP (polyps in the olfactory cleft).

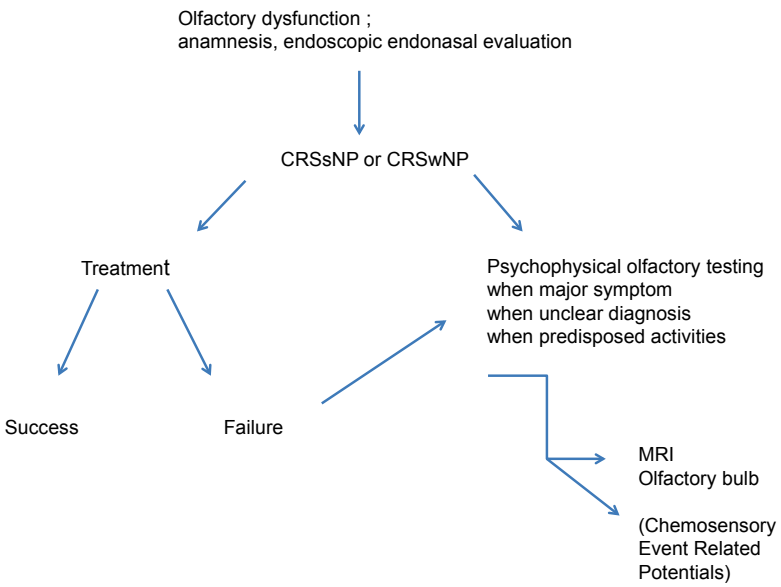
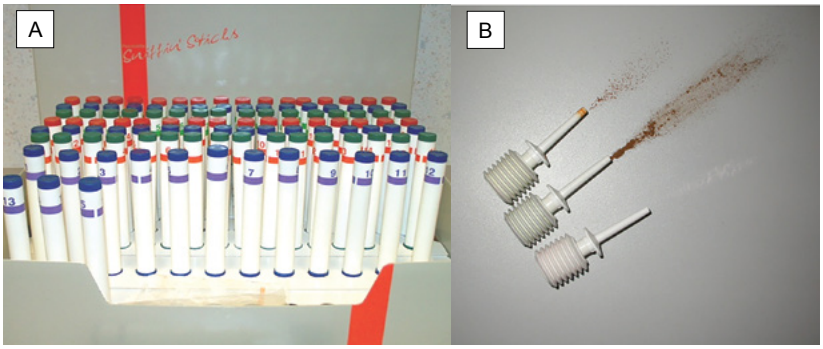


Figure 2 Algorithm for olfactory evaluation in patients with CRS.

semi-objective tests require the collaboration of the patients and need to be age and sex-related to allow distinction between normosmia, hyposmia and anosmia. Retronasal olfactory performances can also be evaluated following a standardized method using powder substances delivered inside the oral cavity using an identification task. A more objective way to determine the olfactory function facilitated by electrophysiological techniques and by chemosensory evoked potentials recording. This technique is based on the fact that a brief olfactory stimulus elicit transient changes in the ongoing electrographic activity. To evaluate the olfactory function a pure odorant substance (i.e. 2-phenylethanol) is delivered in the nose of the patients. Brain responses are then recorded and averaged and responses are transformed into a single waveform called the olfactory event-related potentials. In CRS, both orthonasal and retronasal scores can be decreased and chemosensory even related potentials may demonstrate subtle changes in the amplitude and/or latency in moderate cases and may be absent in severe cases. Because it is impossible to record olfactory event related potentials in up to one third of the normal subjects, electrophysiological studies need to be interpreted with caution.

Beside CT scanning of the nose and of the paranasal sinuses, the magnetic resonance (MRI) is the imaging modality of choice for the evaluation of the olfactory apparatus since it allows examining the olfactory bulb, olfactory tract and central olfactory projection areas (Figure 4). The assessment of olfactory bulb volume is particularly useful in the evaluation of olfactory disorder with a non sino-nasal origin. For the sino-nasal related olfactory dysfunction MRI may demonstrate changes in the olfactory bulb volume related to the residual olfactory function and more importantly some plasticity when the olfactory bulb volume is increased after a surgical procedure.



Identification tests	Thresholds tests	Identification and Threshold tests	Identification, Threshold and Discrimination tests
University of Pennsylvania Smell Identification Test (UPSIT)(Doty, Shaman et al. 1984)	T&T olfactometer(Takagi 1987)	Connecticut Chemosensory Clinical Research Center Test (CCCRC)(Cain, Gent et al. 1983)	Sniffin' Sticks extended test(Hummel, Sekinger et al. 1997; Hummel, Kobal et al. 2007)
Smell diskettes test(Briner and Simmen 1999)	Alcohol Sniff Test (AST)(Davidson and Murphy 1997)	Combined Olfactory Test (COT)(Robson, Woollons et al. 1996)	Eloit and Trotier Olfactory Test(Trotier, Bensimon et al. 2007)
Odorant confusion matrix(Wright 1987)			Random Test(Kobal, Palisch et al. 2001)
Barcelona Smell Test (BAST-24)(Guilemany, Garcia-Pinero et al. 2009) Retronasal test of olfactory function(Heilmann, Strehle et al. 2002)			

Figure 3 A: Orthonasal test Sniffin's stick test used for treshold, discrimination and identification tasks; B: Retronasal test and some others validated tests.

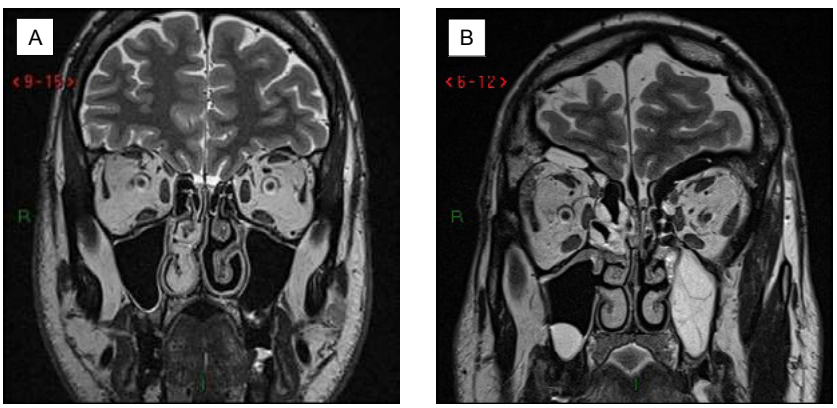


Figure 4 A: T2 coronal MRI showing the Olfactory bulb; B: T2 coronal MRI showing the olfactory bulb in CRS

Topical corticosteroid (spray, drops, squirt, aerosol) and oral corticoid may help to restore the olfactory function in CRS patients. Usually, this positive effect is incomplete and transient and more efficient when the drug reaches the olfactory. Surgery such as endoscopic endonasal surgery is also very helpful and "sandwich" treatment (corticoid/surgery/corticoid) seems to have the better chance to help the patient with an olfactory dysfunction and CRS.

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4 MEDICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Chronic rhinosinusitis (CRS) should be adequately managed for optimal disease control
- Topical corticosteroids and douching are the mainstay of medical treatment in CRS
- Systemic treatment is the second line treatment in CRS patients with severe symptoms
- Antihistamines have a beneficial effect in CRS patients with concomitant allergic rhinitis
- Following the current evolution in CRS phenotyping, more personalized treatments based on the underlying inflammation will most likely be considered in the future
- Treatment with biologicals can only be recommended when additional studies show beneficial effects in (sub)groups of patients with CRS

Chronic rhinosinusitis (CRS) is defined as a symptomatic inflammatory process of nasal cavity and paranasal sinuses with or without the presence of nasal polyps (NP), for at least 12 weeks. The presence of nasal congestion or blockage, discolored rhinorrhea or postnasal drip, facial pain or pressure, hyposmia or anosmia together with consistent pathologic findings during nasal endoscopy or on CT scan establishes the diagnosis. Currently, a variery of therapeutic protocols have been developed and recommended for CRS: topical and systemic corticosteroids, short- or long-term antibiotics, nasal irrigation, decongestants, antihistamines and even allergen immunotherapy (when allergy is confirmed by specific IgE measurement), antileukotrienes, (Figure 1, Figure 2).

Topical intranasal corticosteroids (INS) and nasal douching are first-line treatment for CRS. Nasal douching clears the sinonasal cavity from pathogens and pro-inflammatory mediators. INS target the inflammatory response underlying nasal congestion, promote osteomeatal complex drainage and occasionally improve the sense of smell. Moreover, a significant reduction in polyp size in cases of CRS with NP (CRSwNP) has been reported. Based on clinical experience, systemic corticoids remain important for the treatment of CRSwNP, as they provide short-term symptom relief. Short term courses of oral corticosteroids are usually given two to three times yearly.

Oral antibiotics together with topical corticosteroids have been proven to act synergistically, though antibiotics are reserved for the acute exacerbations of CRS. Low-dose macrolides have been used as a long-term antibiotic treatment in CRS, while topical antibiotics remain an option for refractory cases where traditional topical steroids and oral antibiotics are ineffective.

Nasal irrigation (douching) is a safe, inexpensive method with beneficial effects such as improvement in mucous clearance, enhanced ciliary beat activity, removal of antigens, biofilms or inflammatory mediators. Intranasal decongestants like xylomethazoline improve sinus ventilation through nasal decongestion, though prolonged use may have an opposite effect resulting in rhinitis medicamentosa.

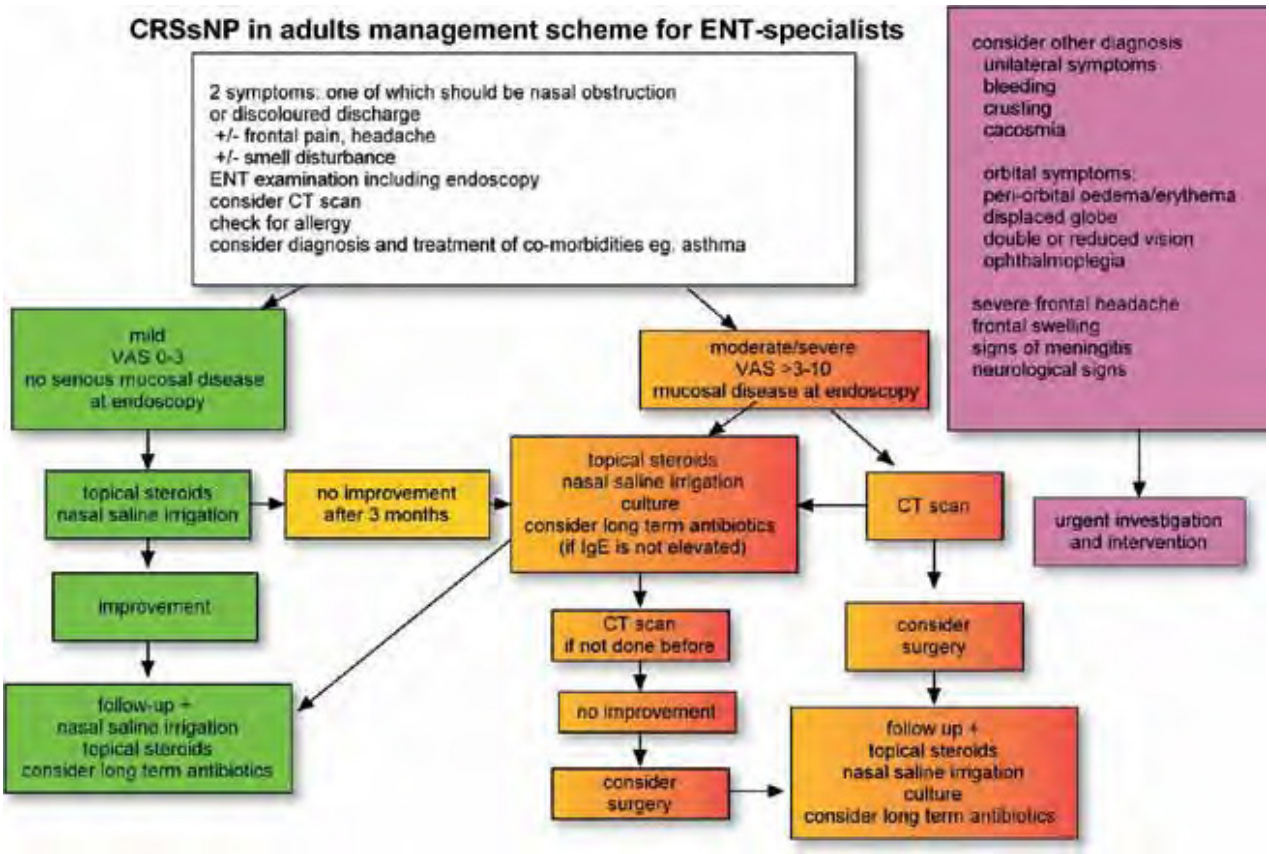

Figure 1 Management scheme for adults with CRS without NP for ENT specialists.

Antihistamine have a minimal beneficial in CRS patients with concomitant AR. According to the GAL²EN study, approximately, 57% of patients with CRS report symptoms of allergic rhinitis (AR) as well. The correlation with asthma is stronger in those patients with both CRS and AR symptoms. In the absence of AR, CRS has a positive correlation with a late onset asthma. To sum up, checking for allergy is advocated in CRS patients. Antileukotrienes (montelukast) might have a beneficial effect in patients with NP.

Following the current evolution in phenotyping, more personalized treatments based on the underlying inflammation will most likely be considered in the future. Recent insight into B cell differentiation into IgE-secreting plasma cells in CRSwNP help to understand the phenomenon of localized IgE production in NP without correlation to systemic IgE levels or to SPT results.

The results of clinical trials suggest that anti-IL-5 antibodies like reslizumab could play a role in the treatment of selected CRS patients with NP. Given the cost of targeted treatments with monoclonal antobodies, they will probably be used for severe recurrent NP associated with difficult to control asthma. Considering local production of IgE antibodies in NP, it appears that local IgE is functional in the regulation of chronic inflammation. So, methods to antagonize IgE antibodies could be of relevance. Omalizumab, a recombinant DNA-derived humanized IgG monoclonal antibody has been studied and approved for asthmatic patients. Up to date omalizumab is not recommended for patients with NP. Future randomized controlled trials for further evaluation of benefit of therapies with anti-IL-5 and anti-IgE are required.

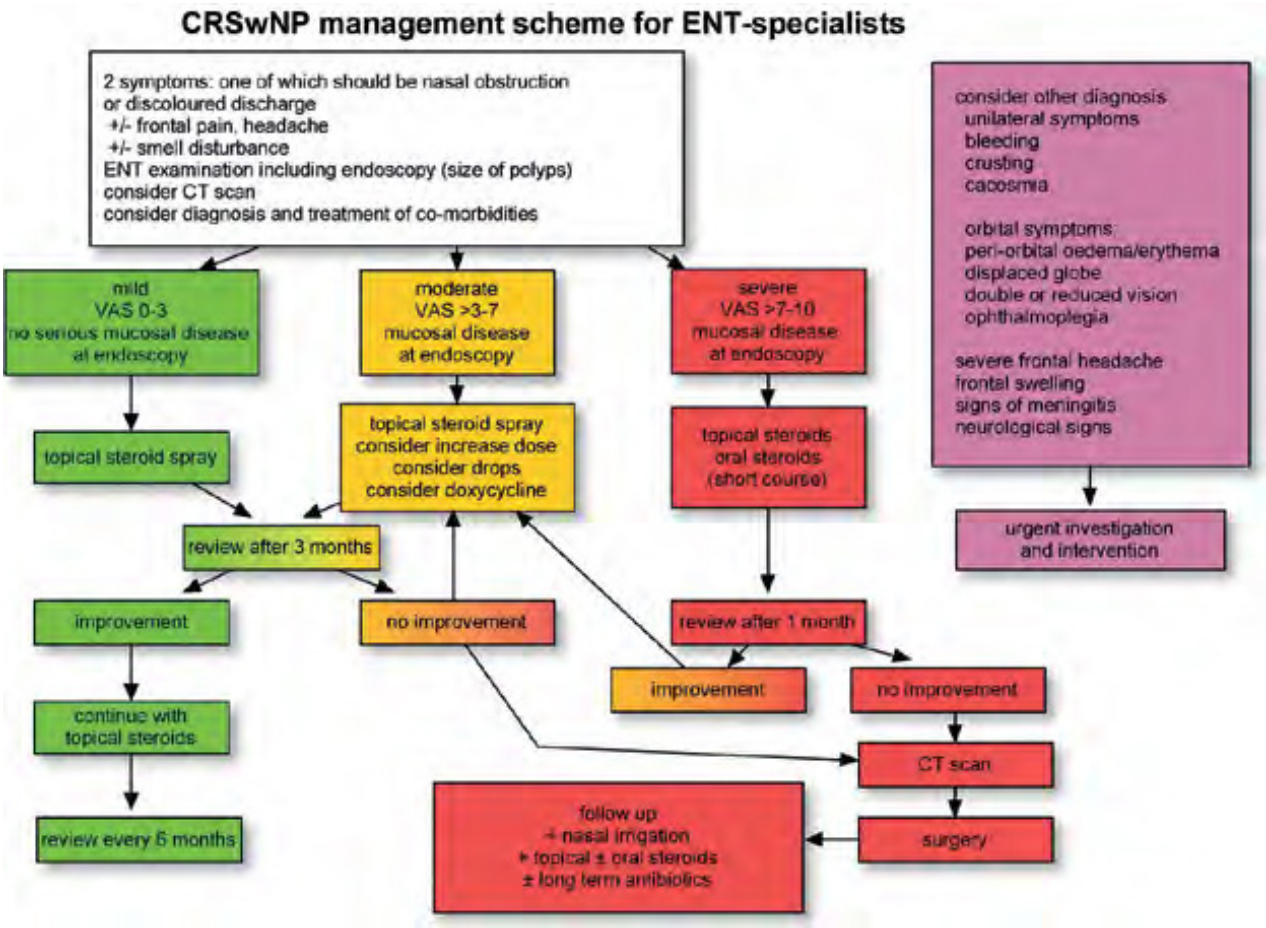

Figure 2 Management scheme for adults with CRS with NP for ENT specialists.

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5 TOPICAL AND SYSTEMIC CORTICOSTEROIDS IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- There is good evidence that intranasal corticosteroids (INS) are a beneficial treatment for both chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP)
- Oral corticosteroids are also effective for the management of CRSwNP, but the short-lived benefits of systemic corticosteroid therapy need to be balanced with the potential side effects
- Postoperative treatment with corticosteroids is strongly recommended in CRSwNP to prevent relapse
- The powerful anti-inflammatory effects of corticosteroids in CRS are mediated by the binding and activation of intracellular corticosteroid receptors expressed in all human cells and tissues

Corticosteroids (CS) are hormones essential for life that are synthesised and released by the adrenal cortex in a circadian manner and in response to stress. Their secretion is controlled by the hypothalamic-pituitary-adrenal axis. CS regulate numerous physiologic processes and aim to maintain homeostasis (Figure 1). CS have powerful anti-inflammatory and immunosuppressive actions. Synthetic derivatives of these hormones have been the mainstay for treating inflammatory diseases such as chronic rhinosinusitis (CRS) and asthma, autoimmune disorders, and hematologic cancers.

USE OF CORTICOSTEROIDS IN CRS

European and international guidelines recommend intranasal corticosteroids (INS) as first-line treatment for CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). Several randomised studies have reported that INS improve the control of sino-nasal symptoms compared to placebo in patients with CRSsNP. However, not all authors demonstrate these findings. It has been reported that direct delivery of the CS to the sinuses has more beneficial effect than simple nasal delivery. There is good evidence that INS are a beneficial treatment also for CRSwNP. They improve nasal symptoms, reduce polyp size and prevent polyp recurrence after surgery. The effect on the polyp size is greater when INS are used in patients who have previously undergone sinus surgery. Importantly, INS are a safe therapy with minimal adverse effects in the management of both CRSsNP and CRSwNP.

Systemic CS are effective for the management of CRSwNP but their use is limited to patients with severe or uncontrolled symptoms. A short-term benefit of a short (two to four-week) course of oral CS (OCS) when compared to placebo has been reported, with an objective reduction of polyp size and a subjective improvement of nasal symptoms and quality of life. No significant adverse effects have been reported with a short course of OCS. However, systemic corticosteroid therapy may potentially provoke suppression of the hypothalamic-pituitary-adrenal axis and affect bone mineral density. Thus, the short-lived benefits of systemic corticosteroid therapy need to be balanced with the long-term potential side effects.

Current guidelines strongly recommend continuing medical treatment with CS postopera-

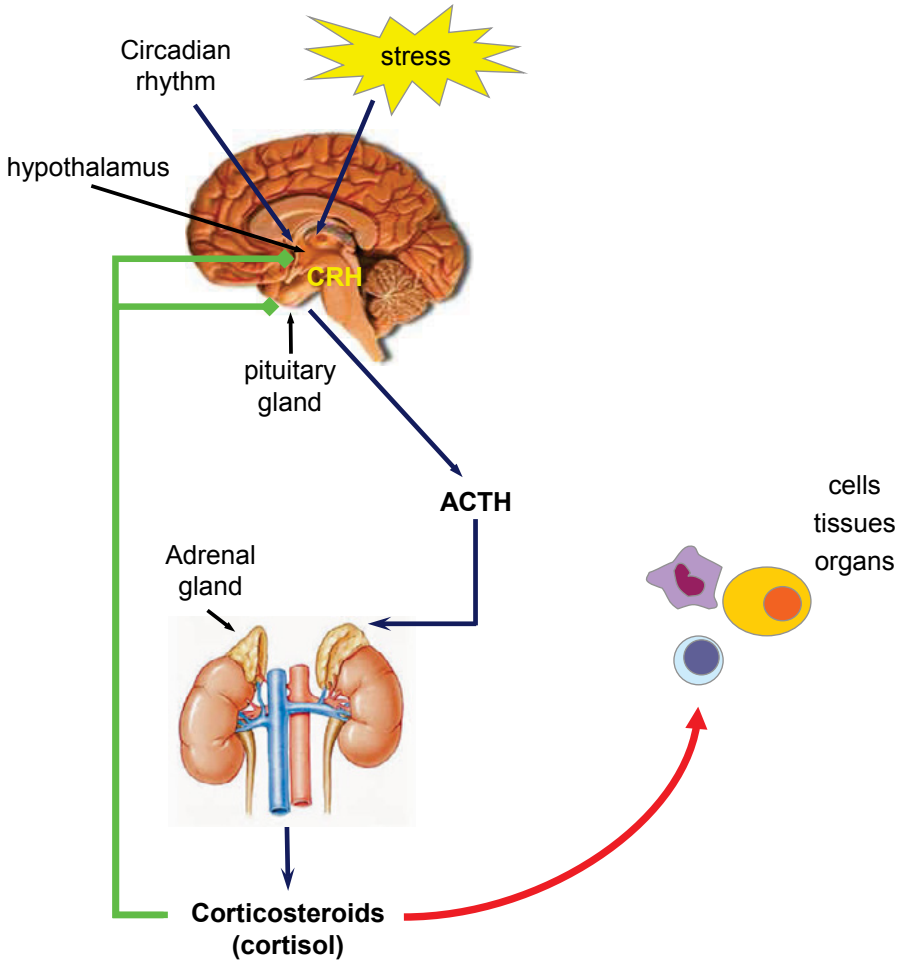

Figure 1 Regulation of corticosteroid (CS) levels by the hypothalamic-pituitary-adrenal axis. Synthesis and release of CS (cortisol in humans) is under daily and dynamic circadian regulation by the periventricular nucleus of the hypothalamus. Corticotropin-releasing hormone (CRH) secreted by the hypothalamus stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, ACTH induces the synthesis and secretion of cortisol from the cortex of the adrenal glands into the bloodstream. CS have effects on numerous cells, tissues and organs. CS regulate their own production by the negative-feedback loop suppressing ACTH levels in the anterior pituitary and CRH levels in the hypothalamus.

tively in patients who have been submitted to endoscopic sinus surgery because they have failed to maximal medical treatment to prevent relapse of the disease.

MECHANISM OF CS ACTION

CS achieve the reduction of nasal symptoms in most patients with CRS because they have powerful anti-inflammatory effects. The clinical efficacy of CS depends in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation. CS also have important effects on the sino-nasal epithelial cells with reduction of the secretion of chemotactic cytokines and other proinflammatory mediators (Figure 2).

The biological action of CS occurs after their binding to the intracellular CS receptors (GR) expressed in all human cells and tissues, including in the sinonasal mucosa. The CS-GR complex rapidly translocates into the nucleus and modulates, either positively or negatively, the expression of target genes (Figure 3). Thus, CS activate the expression of several anti-inflammatory genes, such as the

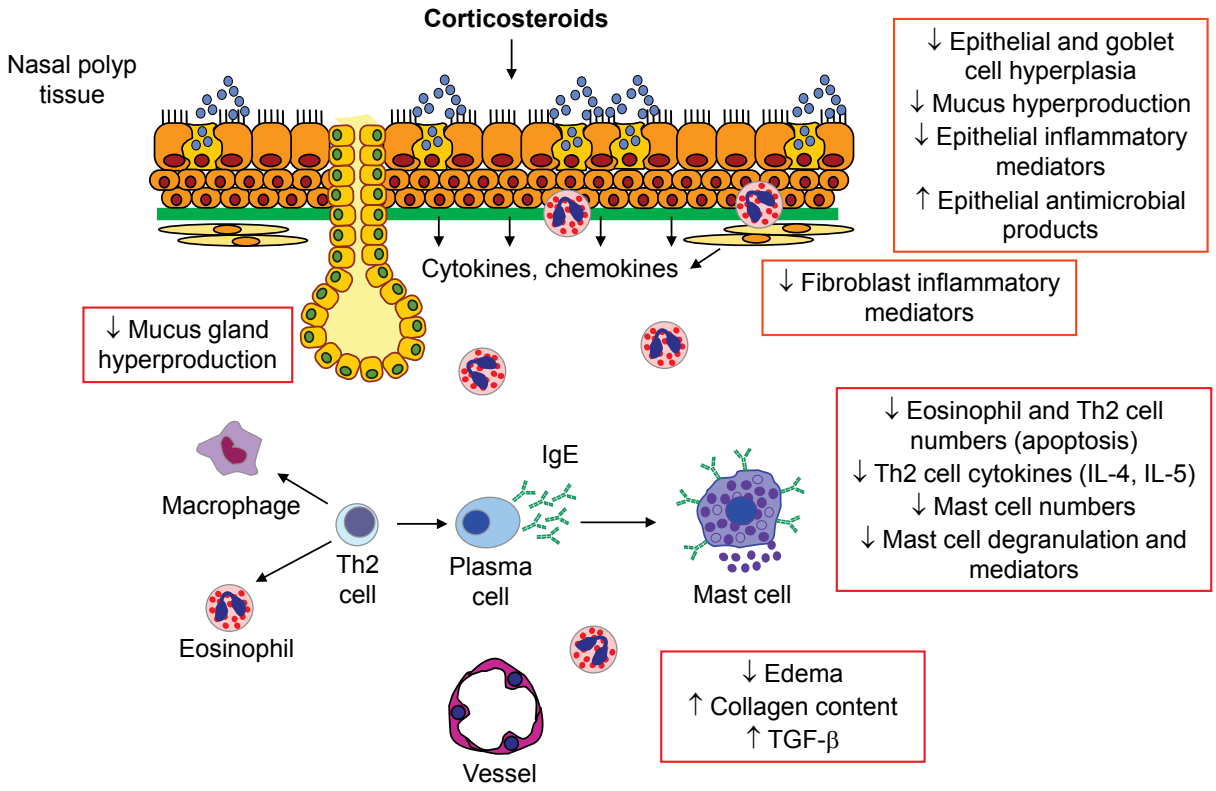

Figure 2 Schematic representation of the effect of corticosteroids (CS) on the epithelium and submucosa of an eosinophilic nasal polyp tissue. The effect of CS on the different cells and mediators involved in chronic rhinosinusitis with nasal polyps (CRSwNP) pathogenesis is shown in red boxes.

mitogen-activated protein kinase (MAPK) phosphatase-1 (MKP-1) and the glucocorticoid-induced leucine zipper (GILZ). The GR-CS complex also suppresses the transcription of numerous cytokines, chemokines and other proinflammatory mediators through the blockade of proinflammatory transcription factors, such as activating protein-1 (AP-1) and nuclear factor-κB (NF-κB).

Interestingly, a lower expression of the GR has been reported in nasal polyps from CRSwNP patients compared with the control nasal mucosa, and a lower anti-inflammatory activity of the GR has been reported *in vitro* for fibroblasts sampled from patients with CRSwNP and asthma compared with the control nasal mucosa fibroblasts.

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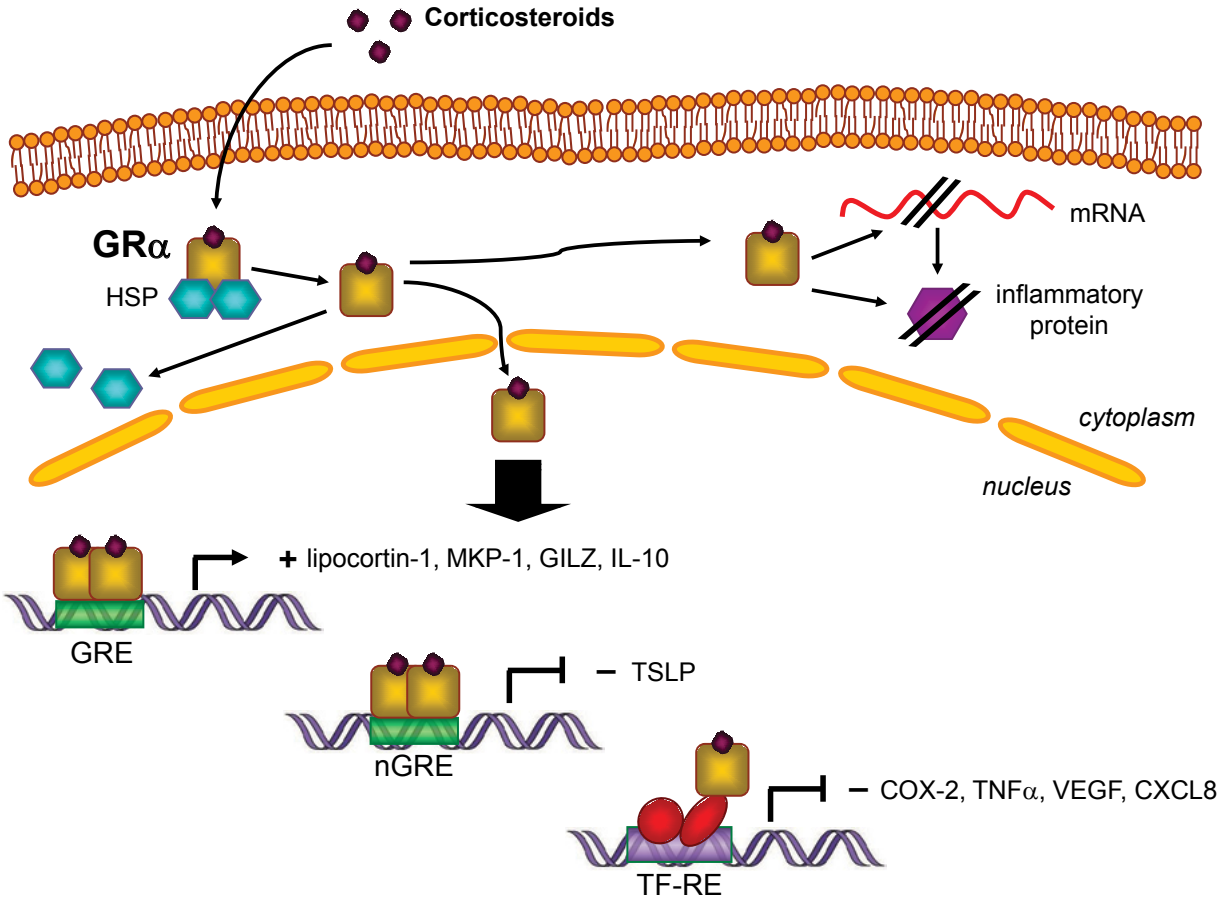

Figure 3 Mechanisms of corticosteroid (CS) action. After passing the cell membrane by passive diffusion, corticosteroids bind to CS receptor α (GRα), associated heat-shock proteins (HSP) are released, and the CS-bound receptor translocates into the nucleus. The receptor can bind CS responsive elements (GRE) on the promoter region of target genes and activate gene transcription; it can bind to negative GRE (nGRE) and lead to transcriptional repression; it can physically interact with pro-inflammatory transcription factors such as NF-κB and AP-1 and repress the transcription of pro-inflammatory genes. The receptor can also alter the mRNA or protein stability of inflammatory mediators. TSLP: thymic stromal lymphopoietin, COX-2: cyclooxygenase-2, TNF-α: tumor necrosis factor, VEGF: vascular endothelial growth factor, CXCL8: chemokine (C-X-C motif) ligand 8 (or IL-8), TF-RE: transcription factor-response element. (*Modified from Pujols L, Mullol J, Picado C. Glucocorticoid receptor in human respiratory epithelial cells. Neuroimmunomodulation 2009;16:290-299 and Pujols L, Mullol J, Picado C. Importance of glucocorticoid receptors in upper and lower airways. Front Biosci (Landmark Ed) 2010;15:789-800.*)

6 LONG-TERM USE OF ANTIBIOTICS IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Randomised controlled trials on the efficacy of long-term antibiotics in large and well defined populations with chronic rhinosinusitis (CRS) are lacking
- Patients with normal serum IgE and a low CT score are more likely to respond to macrolides
- The potential cardiotoxicity of macrolides in patients with long QT-syndrome should not be ignored
- Doxycycline and trimethroprim-sulfamethoxazole may provide an alternative to macrolide antibiotics, but randomised controlled trials are lacking
- The immuno-modulating properties of certain antibiotics need further studies and could provide an alternative to corticosteroids in the future

Although chronic rhinosinusitis (CRS) is mainly inflammatory in its' nature, oral antibiotics have for decades been the mainstay treatment.

Macrolide antibiotics such as erythromycin, clarithromycin, roxithromycin and azithromycin are the most studied antibiotics for CRS treatment. Apart from reducing the number of bacteria considered pathogens, other mechanisms of action are not fully understood. Macrolide antibiotics have exhibited *in vitro* strong anti-inflammatory effects, on parity with prednisolone. The anti-inflammatory effects can also be demonstrated by measuring inflammatory mediators in nasal lavage fluid of patients, but if this is secondary to reduced bacterial load or a primary anti-inflammatory effect is not clear. A more speculative explanation is that antibiotics in long-term use prevent pathogenic bacteria to invade the epithelium. Reducing the number of toxins, such as those released by some Staphylococci species is another possible explanation.

There are two placebo-controlled studies using long-term macrolide antibiotics in CRS with conflicting results. Both studies are of the about the same size (n=64 vs 60 patients included). One study showed significant effects on the Sino-Nasal Outcomes Test (SNOT-20), nasal endoscopy, saccharine transit time and IL-8 in lavage fluid with a response rate of 67% in the roxithromycin group vs 22% in the placebo group. In the other study the response rate (44 % in the azithromycin group and 28 % in the placebo group) did not reach significance. The difference between the results of the two studies can be explained by the inclusion criteria, the positive one including only CRS without polyps, whereas the negative one included CRS patients with nasal polyps (CRSwNP) as well. The positive study showed that patients with normal serum IgE are more likely to respond to treatment (Figure 1).

Doxycycline has been compared to methylprednisolone or placebo in CRSwNP over a 20 days treatment period in 47 patients. Both treatments reduced the size of polyps, the effect more pronounced with methylprednisolone, but more long lasting with doxycycline. Cytokines in nasal lavage were affected in different ways suggesting different mechanisms of action.

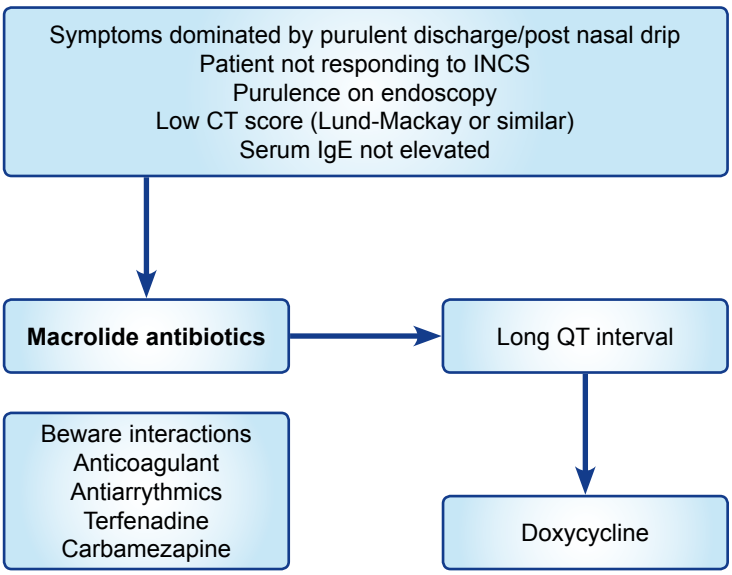

Figure 1 A more likely patient to respond to long-term antibiotic treatment have signs and symptoms dominated by a neutrophilic inflammation such as purulence, normal IgE and a low CT score. Interactions of macrolides with other drugs need to be taken into account and monitoring the serum levels of anticoagulants, carbamezapine etc., may be necessary. As a precaution macrolides should be avoided in patient with a long QT interval.

Another treatment option includes trimethroprim-sulfamethoxazole. A retrospective study in 79 patients with difficult to treat CRS compared macrolides with trimethroprim-sulfamethoxazole and found after at least 6 months of treatment a response rate of 78 % with no difference between the treatment groups. However a placebo arm is lacking.

To sum up, systemic antibiotics have shown effect on symptoms and inflammatory markers in subgroups of CRS patients, but the mechanism of action is unclear and choosing the responsive patient remains challenging. There are also concerns about antibiotic resistance and significant drug interactions as well as a concern for cardiac events with macrolides, especially in patients with long QT syndrome (Figure 1).

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7 IMMUNE MODULATION IN CHRONIC RHINOSINUSITIS

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Chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP) incorporates a heterogeneous group of disorders differing in aetiological and exacerbating factors, while CRS with nasal polyps (CRSwNP) is a more distinct immunological disease with Th2 dominance accompanied by excess IL-5 expression and high levels of IgE and tissue eosinophilia. Allergic fungal rhinosinusitis (AFS) (Figure 1) is a distinct subset of CRSwNP, with both type 1 IgE mediated hypersensitivity and type 3 IgG mediated responses to fungal hyphae. Both CRSwNP and AFS have understandably received more focus in terms of the immunomodulation.

In order to assess the role of immune modulation in CRS Pubmed/Embase and the Cochrane database were searched using the following terms: (Sinusitis or nasal polyp) and (aspirin or salicylate) and; (Sinusitis or nasal polyp) and (immunotherapy or immunomodulation) and; (Sinusitis or nasal polyp) and (monoclonal or anti-IgE pr anti-IL5 or mepolizumab or omalizumab). In total 1103 abstracts were reviewed, and controlled trials and systematic reviews were retrieved.

KEY MESSAGES

- Aspirin desensitisation appears to be beneficial in aspirin sensitive chronic rhinosinunisitis with nasal polyps, but the high rate of adverse events limits its' usage
- Limited evidence supports a role of immunotherapy for allergic fungal rhinosinusitis
- Monoclonal antibodies against IgE and IL5 have been found to reduce polyp size but high cost is likely to restrict the therapeutic use to severe CRSwNP

ASPIRIN DESENSITISATION IN CRSwNP AND ASPIRIN EXACERBATED RESPIRATORY DISEASE

Aspirin-exacerbated respiratory disease (AERD) is an eosinophil dominated inflammatory disease characterized by CRSwNP and asthma, caused by abnormalities in arachidonic acid metabolic pathway. Aspirin desensitisation, achieved through repetitive dosing with oral or topical nasal aspirin, has been used to reduce the recurrence of nasal polyps, occurring frequently. A systematic review of the literature was published in 2013, summarising 11 studies, of which 7 (all observational cohort studies) recommended aspirin desensitization. However, only one study was a randomized trial of nasal lysine aspirin and found no significant ben-

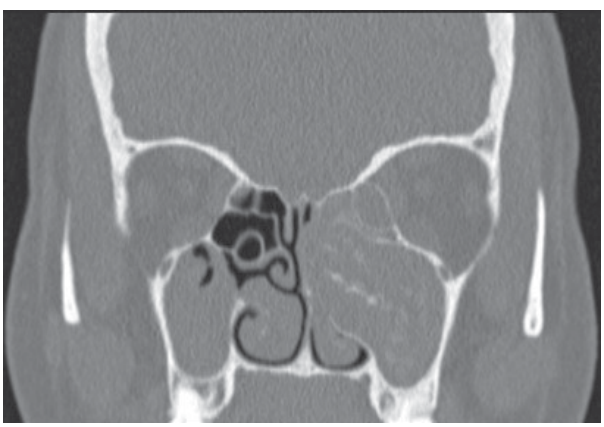

Figure 1 CT scan demonstrating typical features of AFS.

TABLE 1

Summary of evidence for aspirin desensitization

Study	LE (mg)	Route	Dose	F/U	Outcomes(mg)	Adverse effects discontinued RX	Recommend
Swierczynska 2014	1b	po	625	0.5	Sig improvement in Symptom score and ACT	25%	Yes
Fruth 2013	1b	po	100	3	sig imp on nasal polyp recurrence, polyp grade and symptom scores		Yes
Havel 2013	2	po	500	>1.5	sig imp in polyp grade and symptom scores	5%	Yes
Forer 2011	2	po	1050	1	sig imp in olfaction but high drop out rate lead to low power	37%	
Katial 2010	2	po	1100	0.5	sig imp in symptom scores	0%	Yes
Rozasi 2008	2	po	100/ 300	1	300 mg – sig imp in symptom scores polyp grade and decreased surgery 100 mg no benefit	0%	Yes
Lee 2007	2	po	1100/ 650	1	Sig imp in symptom score, reduction in surgery and steroid usage	1100 mg=12% 650 mg=20%	Yes
Berges-Gimeno 2003	2	po	1100	1	Sig imp in symptom score, reduction in surgery and steroid usage	24%	Yes
Gosepath 2001	2	po	100	1	no statistical analysis	0%	?
Stevenson 1996	2	po	1100	1	Sig imp in symptom score, reduction in surgery and steroid usage	13%	?
Ogata 2007	2	nasal		0.25	Sig decrease in polyp size, insig Change in symptom scores		
Parikh 2005	1b	nasal		0.5	No sig differenve in symptom score		No

efit. Two randomized controlled trials have been published since 2013 and both identified significant benefit from desensitization compared with placebo in terms of symptom scores, and one found a benefit in terms of reduced polyp recurrence and further surgery (the other did not report this). Both studies suffered from a high drop out rate (55 and 31%) in part due to adverse effects. The key outcomes of the trials reported are summarized in Table 1.

Aspirin dosages used in published studies vary from 100 – 1100 mg per day, and only one trial has compared different dosages to date.

Given the evidence retrieved there is a low GRADE recommendation for the use of aspirin desensitization for CRSwNP and AERD. The quality of evidence is high, however there is a high risk of harm with high rates of adverse effect leading to drug discontinuation.

IMMUNOTHERAPY IN ALLERGIC FUNGAL SINUSITIS

Even if a strong immunological basis for AFS was documented, there is a paucity of strong evidence supporting the use of immunotherapy, and to date there are no placebo-controlled randomized trials. Two case-control studies, comparing a total of 47 patients undergoing immunotherapy with 35 controls, showed reduced corticosteroid usage, reduced polyp recurrence and decreased need for repeated interventions in AFS patients receiving immunotherapy. A later study by the same group failed to detect a significant difference between active and control groups, but may have been underpowered (n=17). There has been some concern reported of the potential for adverse effects due to immune complex deposition, however one recent small study found no difference in adverse events between AFS and CRS without fungal hypersensitivity following high-dose immuno-

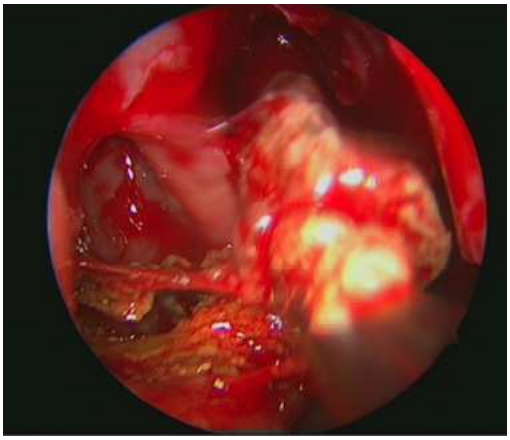

Figure 2 Fungal mucin being removed during surgery for AFS.

therapy. Larger, randomized trials are required to assess both safety and efficacy. All studies to date have assessed the response to immunotherapy in the early post-operative period, with the exception of one study in which 5 patients who received treatment prior to surgery underwent radiological and symptomatic deterioration during treatment. Therefore, immunotherapy should be seen as an adjunct to surgery, which remains the primary treatment modality, removing the allergic mucin (Figure 2) and opening the sinuses to topical therapy.

Given the evidence retrieved there is a low GRADE recommendation for the use of immunotherapy for AFS based on low quality of evidence and low risk of harm.

ALLERGEN SPECIFIC IMMUNOTHERAPY IN PATIENTS WITH CRS AND ALLERGIC RHINITIS

Only 3 case control studies have evaluated the benefit of allergen specific immunotherapy (AIT) for inhalant allergens in patients with co-morbid CRS and allergic rhinitis (AR) with respect to CRS outcomes. All reported better CRS outcomes in patients receiving AIT for their AR after surgery, but have significant methodological flaws or lack adequate statistical analysis, such that no conclusions on the benefits of AIT on symptoms of CRS in patients with AR can be made.

Given the evidence retrieved there is a low GRADE recommendation to NOT recommend AIT in patients with CRS and AR for CRS outcomes alone. The recommendation is based on low quality of evidence and low risk of harm.

SPECIFIC IMMUNOMODULATION WITH MONOCLONAL ANTIBODIES

Omalizumab, an anti-IgE monoclonal antibody (mAb) has been used in 2 placebo controlled RCTs. One study randomised 14 patients with CRS (12 of whom had CRSwNP) and a history of prior surgery to active or placebo treatment and found no benefit in terms of radiological or symptom scores at 6 months. The second study included 24 patients with CRSwNP and asthma, and found that polyp grade, symptom and radiological scores improved significantly with omalizumab compared with placebo. One patient receiving active treatment developed lymphoma one year after completing the trial, however pooled data form asthma trials do not support a causal link of omalizumab with malignancy. There is an isolated case-report supporting the use of omalizumab in AFS.

One placebo controlled randomised controlled trial has demonstrated significantly greater reduction in polyp size and radiological scores in patients with CRSwNP receiving mepolizumab, an anti-IL-5 mAb, when compared with placebo.

Long-term data on mAb safety is required, and patient selection needs to be better defined before recommending widespread use of an expensive drug.

Given the evidence retrieved there is a low GRADE recommendation to NOT recommend mAbs for CRA outside of trials. The recommendation is based on high quality of evidence and unknown risk of harm in association with high cost of treatment

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8 EVIDENCE – BASED SURGERY IN CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Systematic reviews of cohort studies, large outcomes studies consistently support the safety and efficacy of functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis (CRS) with nasal polyps (Level of evidence II)
- However, long term follow up suggests a 15-20 % revision rate, with negative prognostic factors including aspririn hypersensitivity and asthma, cystic fibrosis, previous surgery and extensive disease (Level of evidence II)
- FESS is effective in managing most symptoms of CRS, with effect sizes ranging from 0.8 (hyposmia) to 1.7 (nasal obstruction) (Level of evidence III)

The available randomised controlled trials (RCTs) comparing surgical treatment (Figures 1 and 2) with medical treatment for chronic rhinosinusitis (CRS) with nasal polyps CRSwNP are summarised in Table 1. We can state that all the RCT's conclude that surgery is as effective as prolonged and maximal medical treatment; and hence should be reserved for patients who fail conservative management, including systemic and local corticosteroids as well as long term antibiotics.

In a review first published in 2003 and updated in 2006 by Dalziel. he screened 632 articles and evaluated 42 articles published between 1978 and 2005 on the effect of functional endoscopic sinus surgery (FESS) on CRSwNP. A total of 12 329 patients were enrolled in the included studies. As a consistent finding patients judged their symptom 'improved' or 'greatly improved' in 75 to 95 percent (level IV evidence). The percentage of overall complications was 1.4% for FESS compared to 0.8% to conventional procedures.

In 2000 the Clinical Effectiveness Unit of the Royal College of Surgeons of England conducted a National Comparative Audit of

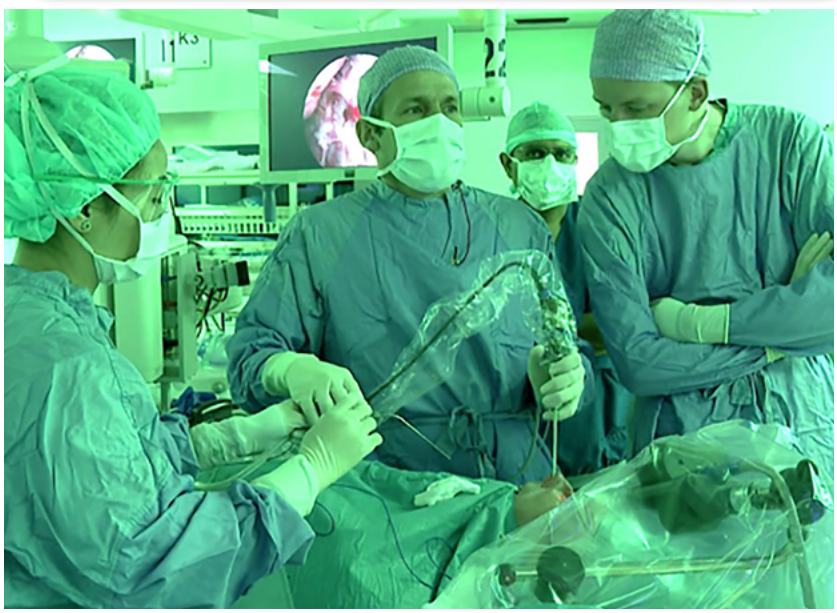

Figure 1 Setup for endoscopic sinus surgery for CRS with nasal polyps.

TABLE 1

Randomized controlled studies comparing surgery with medical treatment in chronic rhinosinusitis with nasal polyps

Author	N	Follow up	Inclusion criteria	Non ESS group	ESS group	Outcome
Lildholdt 1988	53	52 wks	CRS with NP	14mg bethamesone injection followed by 12 months intranasal steroids	Intranasal polypectomy followed by 12 months intranasal steroids	No difference in symptom score
Fairley 1993	33 (29)	6-12 wks	Sinusitis symptoms + endosopic or radiological findings of sinustis	Intranasal antrostomy	ESS	Both groups improved, no difference between groups
Hartog 1997	89 (77)	12-52 wks	Rhinorhea /obstruction/headache and radiological evidence of maxillary opacification	Sinus irrigation + Loracarbef po 10 days	Sinus irrigation+ loracarbef po 10 days + ESS	No difference in overall cure rates, ESS group improved more in postnaasal discharge and hyposmia
Lidholdt 1997	126	2 years	CRS with NP	14mg bethamesone injection followed by 12 months intranasal steroids	Intranasal polypectomy followed by 12 months intranasal steroids	No difference in total symptoms scores or need for medication
Blomqvist 2001	32	52 wks	Endoscopic evidence of CRS with NP	Budesonide spray	Budesonide spray +ESS	Surgical group has bigger improvement in nasal obstruction and discharge, not hyposmia
Ragab 2004	90 (78)	52 wks	2 major or one major and 2 minor symptoms and CT evidence of CRS	3 months of erythromycin + nasal steroid + nasal douche	ESS+nasal steroid + nasal douche	No difference in total symptom scores, greater improvement in nasal volume in surgical group
Blomqvist 2009	32	52 weeks	Endoscopic evidence of CRS with NP	Budesonide spray	Unilateral ESS + budesonide spray	CT scores significantly better in surgery group

Abbreviations: CRS = chronic rhinosinusitis; CT = computer tomography; EES = endoscopic sinus surgery; NP = nasal polyps;

the Surgery for Nasal Polyposis and CRS covering the work of 298 consultants working in 87 hospital sites in England and Wales. Patients undergoing sinus surgery were prospectively enrolled and followed up in this observational study at 3, 12 and 36 months post-operatively using the Sino-Nasal Outcomes Test (SNOT-22) as the main outcome measure. Two thirds of the 3128 patients participating in this study had CRSwNP. All forms of sinus surgery were included though the majority were performed endoscopically. Overall there was a high level of satisfaction with the surgery and clinically significant improvement in the SNOT-22 scores were demonstrated at 3, 12 and 36 months. CRSwNP patients benefited more from surgery than the CRS patients without polyps (CRSsNP). Revision surgery was indicated in 3.6% at 12 months and 11.8% at 36 months. Major complications were rare. Five year follow up results from almost half of the patients of this audit were published in 2009: 19% of patients surveyed underwent revision surgery during these five years, including 21% of patients with CRSwNP compared to 15% of patients with CRSsNP. The mean SNOT-22 score for all patients was 28.2, very similar to the results observed at 36 months

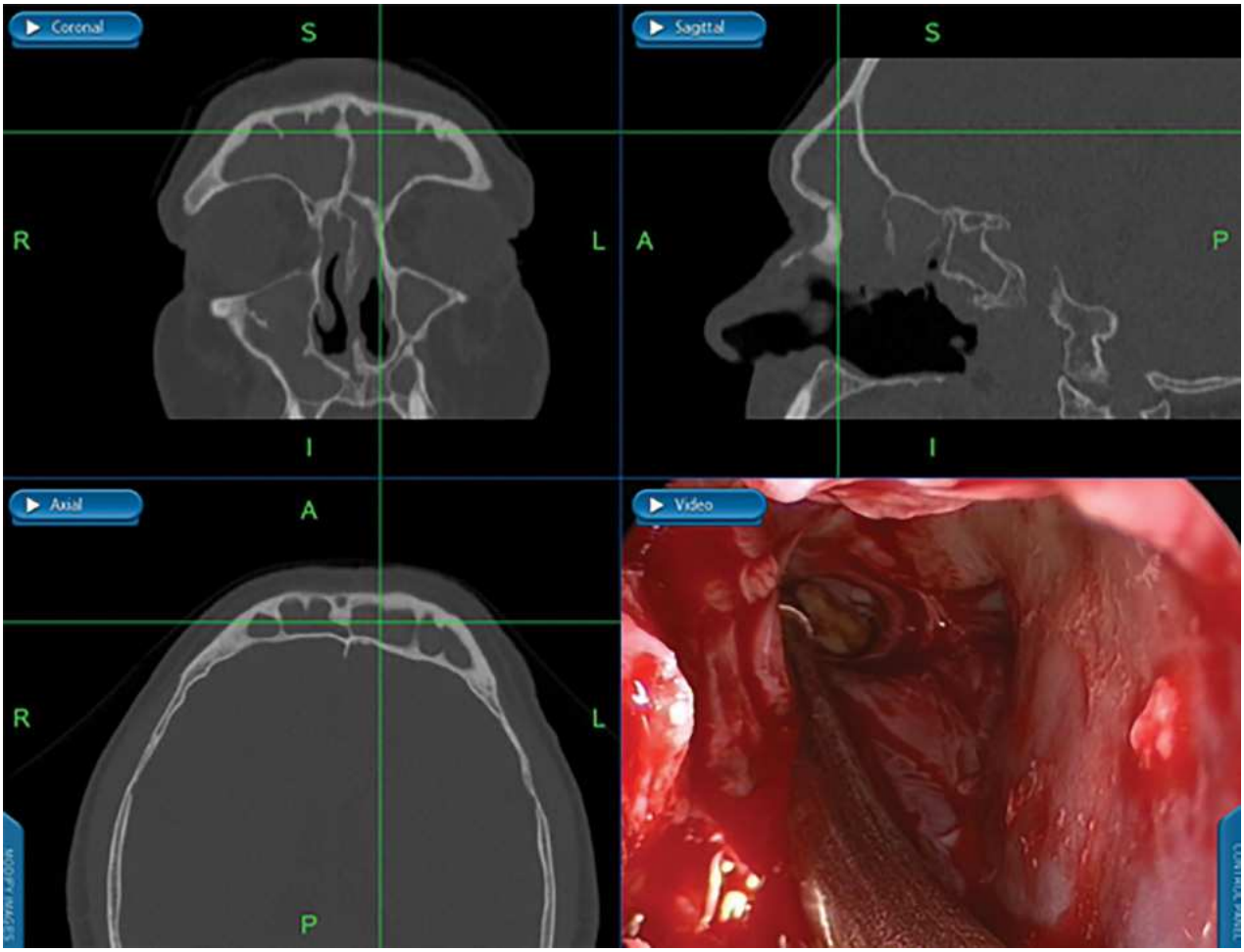

Figure 2 Endoscopic and navigation views of Draf 3 endoscopic sinus approach for extensive sinonasal polyposis.

(27.7), and a consistent 14-point improvement over the baseline score was reported. Scores were better for CRSwNP (mean = 26.2) than for CRSsNP (mean = 33.3) (Level IIc evidence).

A smaller non randomised cohort assessed 180 patients who failed initial medical treatment: 75 of these patients chose to undergo surgery and 75 to continue with medical treatment. Patients who chose to undergo surgery had worse baseline scores but showed more significant improvement in most symptom areas, at one year of follow up, while the same was true for crossover patients.

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9 SURGERY FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS

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KEY MESSAGES

- Endoscopic sinus surgery (EES) is the standard surgical treatment for chronic rhinosinusitis with nasal polyps
- Complete removal of ethmoidal air cells as well as thorough cleaning of the mucosal pathology together with mucosal preservation are key steps for the success of the EES
- Post-operative care such as sinus rinse and/or topical steroids are required to prevent recurrence of the disease

Endoscopic sinus surgery (ESS) has become widespread as a standard and effective surgical method for chronic rhinosinisitis (CRS) (Figure 1). Outcome of ESS for CRS has been further improved by employing post-operative medical therapy including intranasal corticosteroids and low-dose long-term macrolide therapy (Figure 2). Recently, the incidence of CRS with nasal polyps (CRSwNP), which relates to significant eosinophilic infiltration on sinus mucosa, is increasing. CRSwNP tends to show post-operative recurrence of mucosal lesion accompanied by recurrent nasal polyposis (NP), although patient's subjective symptoms are usually improved.

To reduce the frequency of NP recurrence, thorough removal of pathological tissues, especially complete removal of ethmoidal air cells, is required in order to make post-operative local treatments, e.g., topical steroids and sinus rinse, easier. Residual ethmoidal air cells affects outcomes of ESS, because these cells may become a focus of persistent inflammation and/or polyp growth. Another key for better EES outcome is to do "mucosal preservation surgery"3) (Figure 3). Excision of whole mucosa with cup-type forceps is to be avoided as much as possible. Even for irreversible mucosal lesions showing severe edema and hypertrophy, subepithelial lesions are excised with a through-cutting forceps and/or micro-debrider, and the mucoperiosteum should be left intact. Such treatment facilitates ciliated epithelialization of mucosa, and recovery of the ciliary function should occur.

Figure 1 Endoscopic sinus surgery.

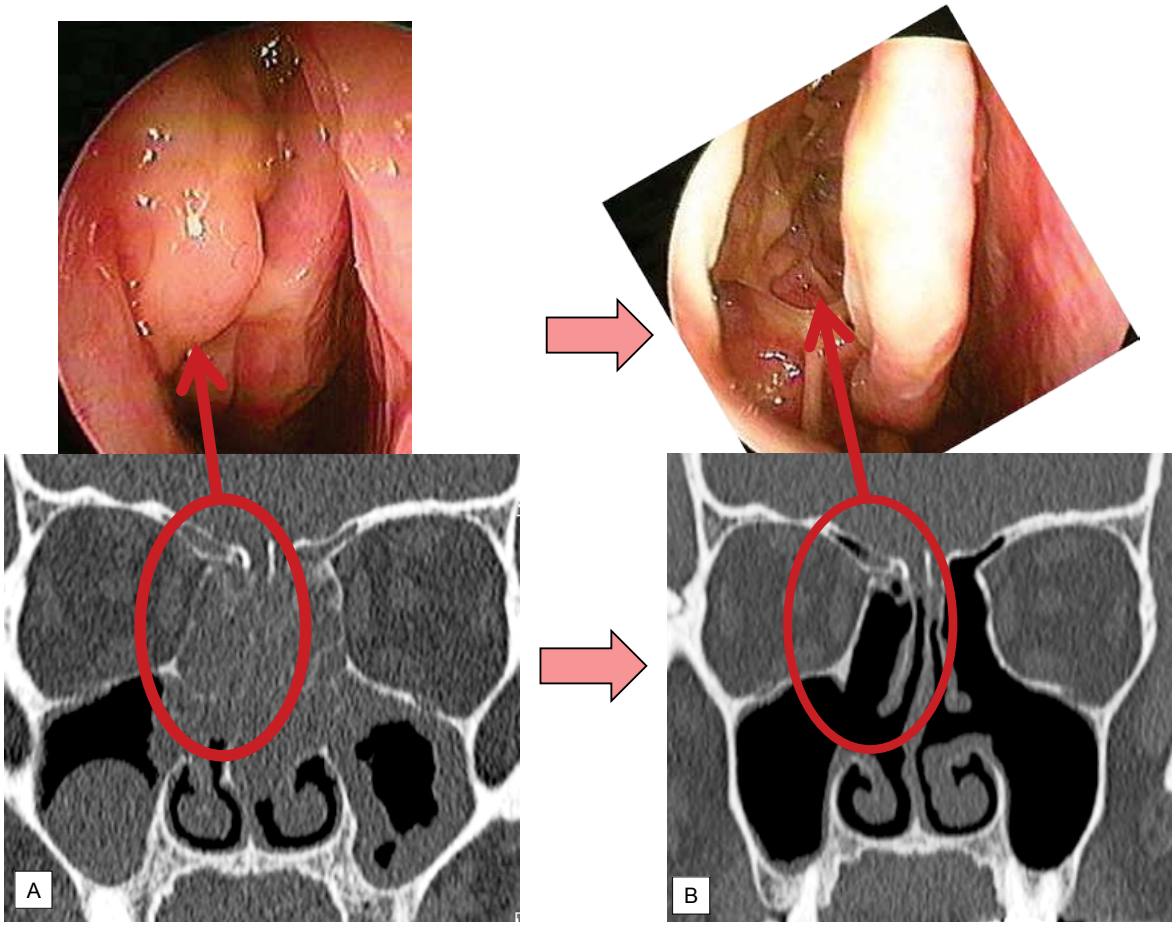

Figure 2 Chronic rhinosinusitis. A-before the surgery. B - after the surgery.

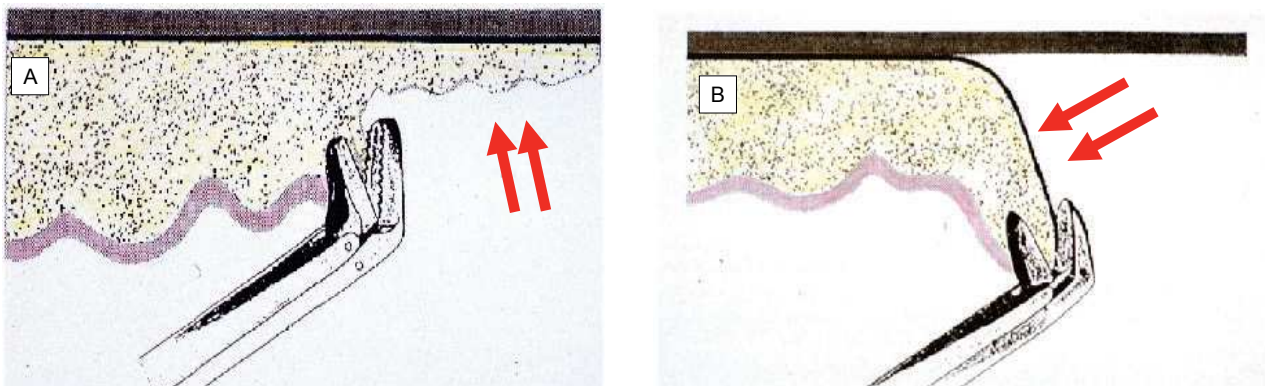

Figure 3 Mucosal preservation. A - mucosal preservation with through-cutting forceps. B - mucosa is not preserved with cup-type forceps.

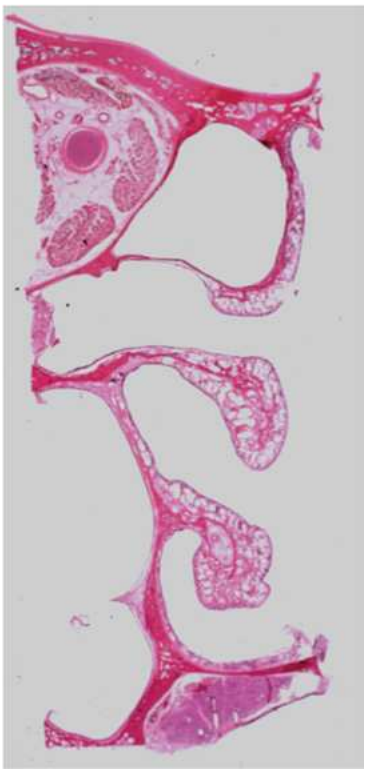

Figure 4 Anatomical preparations of nose, sinus and orbit (right side).

Actual surgical steps are as follows:

1. Nasal polypectomy. NP often derive from the middle meatus and olfactory cleft. These NP should be removed from the bottom.
2. Ethmoidal surgery. Understanding of the location of uncinate process, bulla ethmoidalis, ground lamellae and superior turbinate is important since they serve as an anatomic landmark during the operation. The bone septa in the ethmoid air cells are sufficiently excised to make them as smooth as possible, and a unique cavity is created.
3. Maxillary surgery. The maxillary sinus is inspected with an angled endoscopy, then a curved forceps is inserted through widen maxillary fontanelle to remove the pathologic tissues.
4. Sphenoidal surgery. Entering the sphenoid sinus from natural ostium and posterior ethmoid sinus is recommended with removal of the pathological lesions in the sphenoid sinus, but it is not preferable to remove forcibly a mucosal lesion from lateral or posterior wall
5. Frontal surgery. The approach to a frontal sinus lesion is the most difficult step in ESS. The use of an angled endoscope to look up at frontal recess from below is recommended, since it allows the recognition of the drainage pathway. The angled forceps is inserted carefully to the frontal sinus, and the drainage pathway is enlarged as much as possible. Draf type II or III are chosen to the case of revision surgery or the case of short anterior-posterior diameter.

Inappropriate and rough manipulation during the surgery may cause major complications such as orbital injury and cerebrospinal fluid leakage4. Medical orbital wall is especially thin like a paper (Figure 4). Care must be taken to prevent these complications

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10 INTERFACING MEDICAL AND SURGICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Endoscopic sinus surgery improves the delivery of topical treatment to the sinonasal mucosa
- In chronic rhinosinusitis with nasal polyps, surgically removed polyps have a high tendency for recurrence without aggressive postoperative medical management
- Douching and topical steroid therapy are recommended for control of postoperative mucosal inflammation and should be maintained following endoscopic sinus surgery

Many studies have demonstrated the effectiveness of endoscopic sinus surgery (ESS) for patients who have chronic rhinosinusitis (CRS) with (CRSwNP) or without nasal polyps (CRSsNP). Few studies have also compared medical versus surgical treatment for chronic sinus disease. These studies, including a Cochrane review, show that medical and surgical treatment can lead to similar effects in improving quality of life. Although these trials provide us an interesting insight into the relative efficacies of medical versus surgical therapy they don't provide us sufficient evidence. The comparison medical versus surgical therapy does not reflect current guidelines as it is generally accepted that for both CRSwNP and CRSsNP surgical intervention is only considered in patients who fail to improve after a trial of maximal medical treatment.

If a patient with CRS is considered for surgery it should not be thought of as the only treatment. ESS is rather a surgical technique that decreases the amount of inflammation and creates accessible sinus cavities so that the medical treatment may become more effective. This concept has been proven in CRSwNP patients where patients with previous sinus surgery responded to topical steroid greater than patients without sinus surgery for nasal polyp (NP) size reduction. Patients with NP appear to receive the most benefit of postoperative topical steroids as polyp recurrence rate was reduced and time to polyp recurrence was lengthened. For CRSsNP it is less clear if surgical intervention affects the symptomatic response to a topical steroid. Recent evidence also supports the claim that ESS improves the delivery of topical medications to the sinonasal mucosa, however it should be noted that large volume squeeze bottles or passive flow devices appear to have the best sinus penetration rate.

The fact that there is an important interplay between medical and surgical therapy is also reflected during the immediate perioperative period after ESS. Administration of systemic steroids in the perioperative period for patients who have polyps has a significant impact on their postoperative course. Topical steroids have been shown to improve wound healing after ESS. For antibiotics (both local and systemic) there is conflicting evidence. Two studies evaluating a short and long course of postoperative antibiotics (2 days) demonstrated it had no effect on outcomes, while a third study with a long postoperative antibiotic protocol demonstrated showed a improvement in patient symptoms, endoscopic appearance and significant reduction in sinonasal crust formation.

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11 THE CHALLENGES OF CHRONIC RHINOSINUSITIS MANAGEMENT

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KEY MESSAGES

- Treatment of chronic rhinosinusitis (CRS) is a challenge. Part of the challenge is that CRS represents the end point of multiple etiologic processes that are influenced by genes, environment and age
- The unifying theme for CRS treatment is that inflammation needs to be controlled, acute infections need to be treated with antibiotics, and surgery is reserved for medical failures
- There is large numbers of treatments mentioned in the literature, but there are limited evidence-based publications that support the various treatments
- Many patients do not respond to treatment as indicated by the guidelines
- CRS treatment guidelines are mostly based on expert opinion, do not consider the response to prior treatment or the management of exacerbations, tend to eliminate certain CRS subtypes and do not consider the underlying disease mechanisms

Current guidelines tend to divide chronic rhinosinusitis (CRS) into that with and that without nasal polyps (NP). The guidelines base treatment on the severity of the disease. Unfortunately, most guidelines do not consider the response to prior treatment or the management of exacerbations (Table 1). They tend to eliminate certain subtypes such as cystic fibrosis (CF), antrochoanal polyps, aspirin exacerbated respiratory disease (AERD, fungal disease (allergic and invasive) and complications. Furthermore, children differ from adults in their pathophysiology and thus require different treatment strategies.

The goals of treatment are to eliminate or reduce NP size, restore nasal breathing, restore the sense of smell, reduce symptoms of rhinitis, reduce the number of bacterial infections, and prevent recurrence. In addition, there are suggestions that treatment of CRS improves asthma.

The unifying theme for CRS treatment is that inflammation needs to be controlled, acute infections need to be treated with antibiotics, and surgery is reserved for medical failures (Figure 1).

Treatment with anti-inflammatory drugs is the mainstay, with drugs being given either primarily or secondarily after surgery to slow the rate of recurrence. Because of their anti-inflammatory properties, corticosteroids have been the pillars of treatment. Topical intranasal corticosteroids (INS) are more effective for CRS with polyps than for CRS without polyps. Many clinicians call for more studies regarding the delivery system, to ensure a better distribution of the INS throughout the nose and sinuses. This has been highlighted by the delivery of corticosteroid nasal drops, which reduced the need for surgical intervention in a group of patients who had previously received standard INS. Experience has led to the use of Pulmicort respules® in a Sinusrinse® bottle in the attempt to deliver a large volume of fluid containing a topical corticosteroid into previously operated sinuses and corticosteroid impregnated stents placed at the time of surgery. Oral steroids given over 2 to 4 weeks have been shown to reduce NP size and symptoms, but the optimum dose

TABLE 1

Questions abound for CRS
What phenotype, what treatment?
Do paranasal CT findings define subtypes?
Does allergy play a role?
Does the presence of asthma define a unique phenotype?
How do you define and manage a flare-up of CRS?
When surgery, antibiotics, and steroids fail to resolve CRS, what do we do, (the true unmet need)?

has not been established. In children, oral methylprednisolone added to amoxicillin/clavulanate in the treatment of CRS, improves symptoms and the inflammatory changes on CT scans. The usual clinical treatment of NP is to give oral steroids followed by INS. Intrapolyp injections of steroids were popular until the 1960s, when resulting cases of blindness were reported. Now, this approach has been revisited because some authors report no incidence of blindness with the use of fine suspensions of steroid particles and pre-decongestion. The authors suggest some effectiveness for 4 to 8 weeks and some systemic absorption.

Surgery is clearly indicated for intracranial and intraorbital complications, mucoceles, anatomic variations, allergic fungal disease, massive polyps with bony remodeling, and antrochoanal polyps. The category leading to the majority of surgical interventions, however, is that of patients who remain symptomatic despite medical treatment. Overall, the number of patients requiring surgery is very low. This conservative approach to surgical intervention followed a study showing no difference between medical treatment (INS, douching, and long-term erythromycin) and surgery followed by INS. In support of surgical intervention are the excellent subjective rates of improvement in long-term follow-up. Unilateral surgery showed better CT findings, olfaction, polyp score, and relief of symptoms on the operated side. Several quality-of-life instruments showed better improvement in patients electing surgery compared to those electing continued medical therapy. The best surgical approach has been debated. The currently favored procedure is an extensive surgical clean-out to provide access for topical medicines postoperatively. This concept builds upon the view that INS slow the rate of post surgery recurrence. Surgical revision rates have increased for cases of AERD, asthma, and frontal-sinus disease. Surgery in children is almost done exclusively in patients with CF and those with orbital and intracranial complications. The first surgical approach for children is an adenoidectomy plus/minus a maxillary sinus wash.

The goals of the use of **antibiotics** are to eliminate infection, reduce inflammation, and clear biofilms. The use of topical antibiotics lacks good studies on safety, particularly regarding systemic effects: only 1 of 7 randomized, placebo-controlled studies showed a positive effect. Mupirocin, used in an open study, showed positive effects in *Staphylococcus aureus*-positive patients. Oral antibiotics have been used short-term for treatment of acute episodes of CRS. Studies of the long-term use of antibiotics for their anti-inflammatory properties have had mixed results. In total, topical antifungals have not been shown to be effective in the treatment of CRS.

Because patients have persistent symptoms, besides the above approaches a multitude of **other strategies** have been suggested. These include oral and topical antihistamines, leukotriene receptor antagonists, 5 lipooxygenase inhibitors, anti-IgE and anti-IL 5 monoclonal antibodies, immunotherapy against fungus and other aeroallergens, large-volume irrigations with or without drugs, methotrexate, topical and oral antifungal drugs, decongestants, mucolytics, phototherapy, protein pump inhibitors, capsaicin, furosemide, Vitamin D, Manuka honey, bromelain, N-acetylcysteine, quercetin, undecylenic acid, urtica dioica, massage of sinus ostea with swabs of botanical essential oils, air purifiers, and diets, as well as aspirin desensitization orally or intranasal The vast majority of the use of these treatments is supported by individual experience, and they place emphasis on the group of patients for whom we do not have effective treatment.

In summary, the design and interpretation of CRS clinical trials have been hindered by the inherent heterogeneity of the disease, a lack of uniform definitions for the various subtypes, an incomplete understanding of the underlying pathologies, the use of rescue medications, and a lack of useful and standardized clinical and laboratory endpoints for measurement of the response to therapy.

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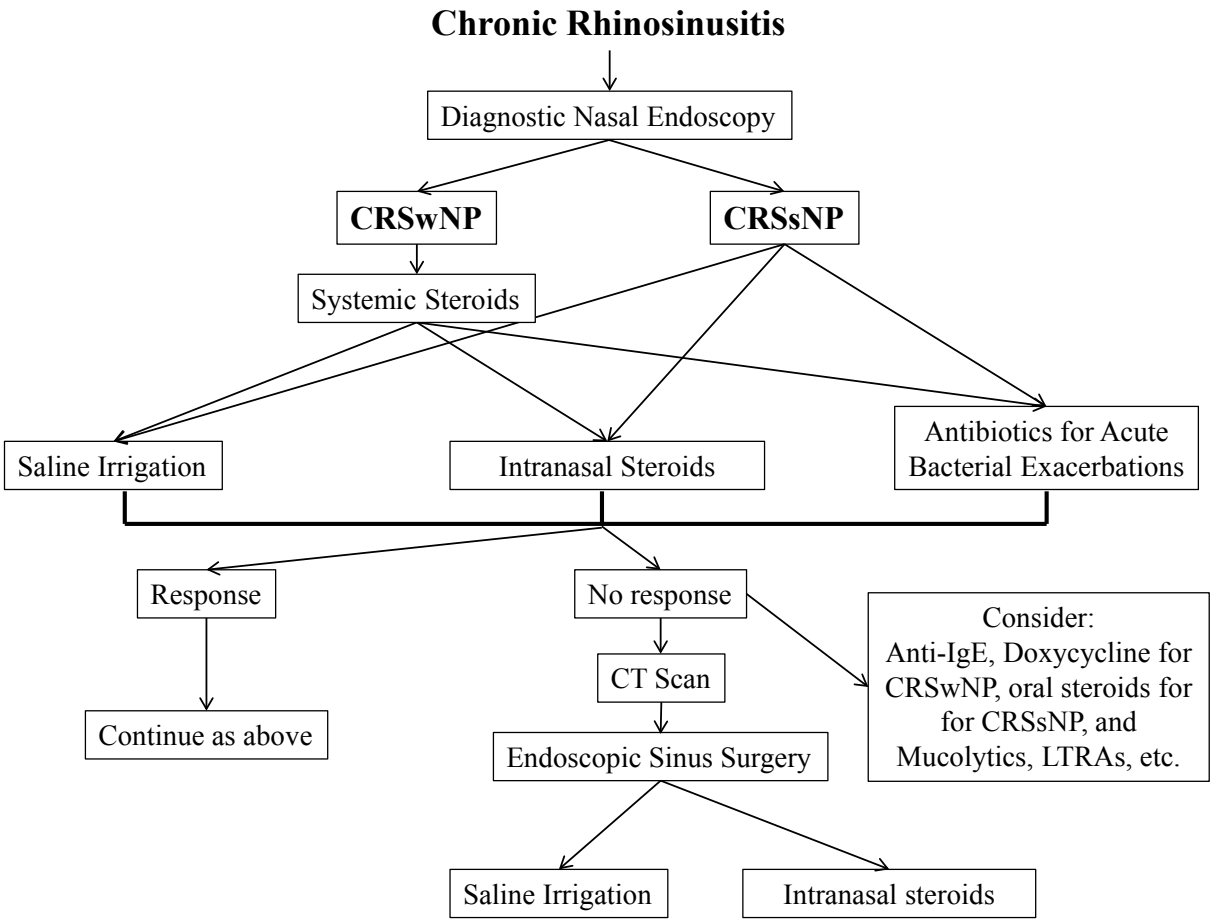

Figure 1 The figure depicts the most supported modes of therapy for chronic rhinosinusitis. Evidence based studies support the use of systemic steroids followed by topical steroids and saline irrigations for patients with chronic rhinosinusitis with nasal polyps (CRSwNP). For patients without nasal polyps (CRSsNP), most evidence supports saline irrigations and intranasal steroids. Antibiotics are reserved for the treatment of acute bacterial exacerbations of the disease with less evidence to support the prolonged use of antibiotics for their anti-inflammatory properties. If the patients respond to the treatment regimen, it should be continued with close clinical follow up. If they do not respond, then a sinus CT scan followed by endoscopic sinus surgery is offered followed by maintenance of a disease free cavity postoperatively with the use of saline irrigations and intranasal steroids. Other less supported agents such as Anti-IgE and Doxycycline for CRSwNP, oral steroids for CRSsNP, and mucolytics, LTRAs, etc can be considered if conventional therapy does not lead to a response.

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Section I

EN

Council conclusions on prevention, early diagnosis and treatment of chronic respiratory diseases in children

3131st EMPLOYMENT, SOCIAL POLICY, HEALTH and CONSUMER AFFAIRS Council meeting

Brussels, 1 and 2 December 2011

TOWARDS A COMPREHENSIVE GLOBAL STRATEGY FOR THE MANAGEMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

* The European Union plan of the early diagnosis and control of chronic respiratory diseases
* ARIA: from a guideline to a care pathway (AIRWAYS ICPs)
* Severe chronic upper airway diseases
* Important research questions in chronic upper airways diseases
* Policies and strategies to facilitate access to diagnosis and treatment for chronic upper airway diseases
* Policies and strategies to reduce risk factors for allergic rhinitis and chronic rhinosinusitis
* The role of primary health care in the management of chronic upper airway diseases
* The role of Patient Organisations in the management of allergic rhinitis and chronic rhinosinusitis
* Comprehensive management plan in allergic rhinitis – Towards a patient-centered attitude
* The role of pharmacists in the management of chronic upper airway diseases
* The role of schools in the management of chronic upper airway diseases
* Managing allergic rhinitis and chronic rhino-sinusitis in developing countries - focus on Latin America
* Managing allergic rhinitis and chronic rhinosinusitis in developing countries – focus on Eastern Europe
* Managing allergic rhinitis and chronic rhinosinusitis in developing countries - focus on Asia Pacific
* Management of allergic rhinitis and chronic rhinosinusitis in developing countries - focus on Africa
* Managing allergic rhinitis and chronic rhinosinusitis in developing and low income countries - focus on South Asia
* Managing allergic rhinitis and chronic rhinosinusitis in developing countries – focus on East Asia
* Best buys for allergic rhinitis and chronic rhinosinusitis prevention and control
* The role of the allergist in allergic rhinitis and chronic rhinosinusitis
* Web-based surveys and monitoring in the management of allergic rhinitis and chronic rhinosinusitis
* Vision, roadmap and land-marking event

1 THE EUROPEAN UNION PLAN OF THE EARLY DIAGNOSIS AND CONTROL OF CHRONIC RESPIRATORY DISEASES

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KEY MESSAGES

- Article 168 of the "Treaty on the Functioning of the European Union" (EU) provides a basis for conducting international health policy
- On this basis, the Council Conclusions on "Prevention, early diagnosis and treatment of chronic respiratory diseases in children" was adopted, defining the strategy of the EU for the chronic respiratory diseases (CRD)
- The EU strategy recommends building national and international policies aimed at the proper prevention, diagnosis and treatment of CRD, science-based and involving international cooperation
- The CC refers to the important role of environmental risk factors such as smoking and air pollution and health inequalities. These factors must be fought. The education of patients and caregivers is also important. These activities aim to allow reducing the socio-economic burden of the disease

In accordance with Article 168 of the Treaty on the Functioning of the European Union (EU) for the protection of human health, documents relating to chronic respiratory diseases (CRD) have been accepted at the international level recognizing them as an important public health problem:

1. Council conclusions of 7 December 2010 on 'Innovative approaches for chronic diseases in public health and health-care systems
2. Council conclusions of 2 June 2004 on childhood asthma

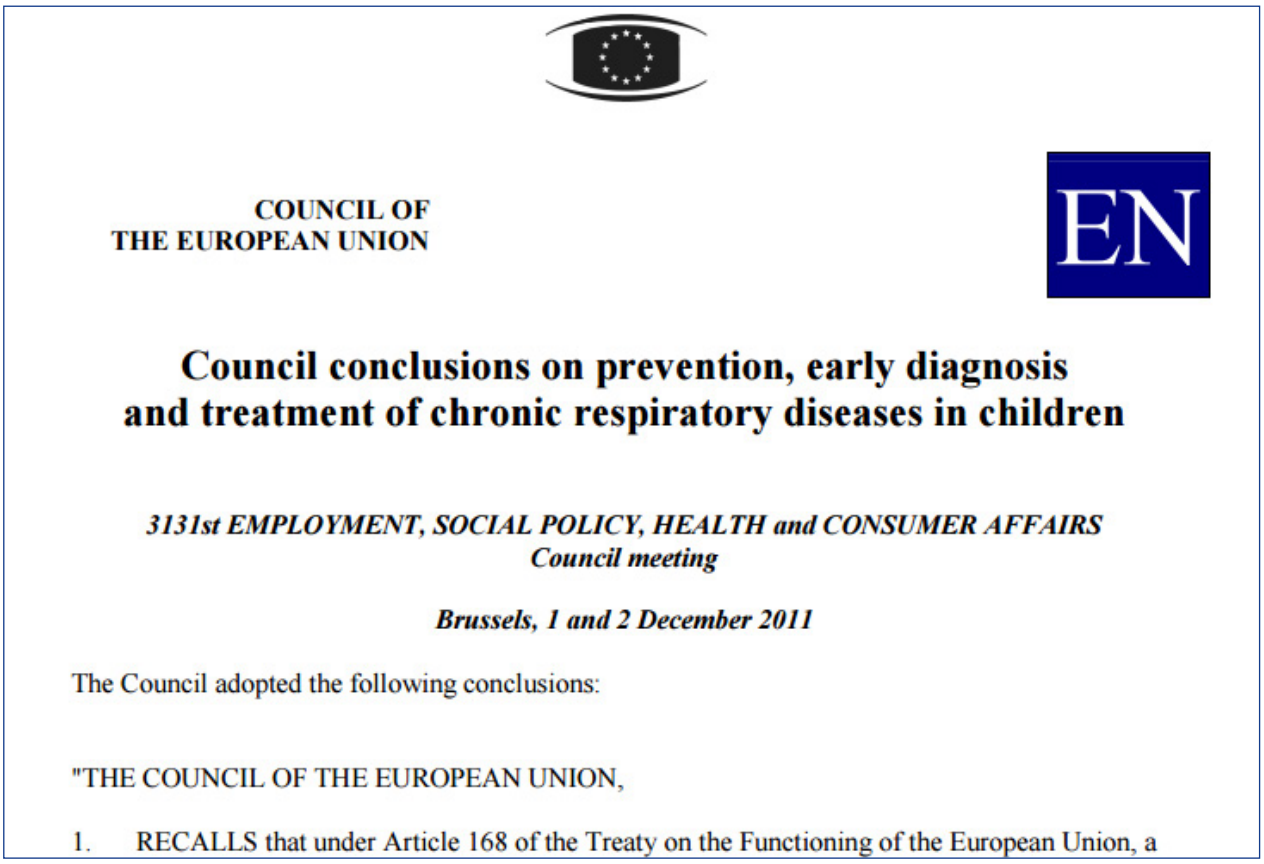
The EU was also a signatory to a number of other documents, especially "Political declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases" adopted by the United Nations General Assembly on 19 September 2011.

The EU Council conclusions on "Prevention, early diagnosis and treatment of chronic respiratory diseases in children" prepared and accepted by 27 Ministers of Health of all European Union Countries during the Polish Presidency of EU in 2011 (Figure 1) play a special role among all mention above documents. This is the first political declaration on so high level concerning CRDs. Its basic contents are summarized as follows:

1. CRDs, especially allergic rhinitis (AR) and asthma, are the most common non-communicable diseases in children
2. CRDs cause lifelong health impairment
3. Both AR and asthma are interdependently and significantly worsen the quality of life of patients,
4. There is a growing number of studies showing that AR and asthma may lead to other chronic diseases (in particular COPD) highlighting the importance for life expectancy and life expectancy in good health
5. Prevention, early diagnosis and treatment by controlling the diseases, environmental factors have a positive impact on the quality of life and active and healthy aging

The Council Conclusions invite the Member States and the Commission to:

- Draw attention to the need for early prevention, diagnosis and treatment of CRD



COUNCIL OF
THE EUROPEAN UNION

EN

Council conclusions on prevention, early diagnosis and treatment of chronic respiratory diseases in children

3131st EMPLOYMENT, SOCIAL POLICY, HEALTH and CONSUMER AFFAIRS Council meeting

Brussels, 1 and 2 December 2011

The Council adopted the following conclusions:

"THE COUNCIL OF THE EUROPEAN UNION,

1. RECALLS that under Article 168 of the Treaty on the Functioning of the European Union, a

Figure 1 Council conclusions of 2 December 2011 on "Prevention, early diagnosis and treatment of chronic respiratory diseases in children".

- Improve the knowledge and education of children, families, teachers and health professionals
- Strengthen the cooperation and support of the national centers, international research networks, patients and healthcare professionals' organizations at all levels of care, to primary and secondary prevention
- Find cost-effective procedures and using health technology to improve health care systems standards regarding to CRD, reduce air pollution and tobacco smoke, improve physically activity, improve exchange best practices
- Encourage and support research on the causative genetic and environmental factors of CRD to contribute to the development of evidence-based policy approaches
- Promote a multisectoral approach across the social, environment, research, education and employment sectors, to improve the impact of policy on respiratory health.

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2 ARIA: FROM A GUIDELINE TO A CARE PATHWAY (AIRWAYS ICPS)

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European Innovation Partnerships (EIP) attempt to enhance European Union competitiveness and tackle societal challenges by fostering innovation.. The Action Plan B3 of the EIP on AHA is devoted to integrated care pathways for chronic diseases across the life cycle. The integrated care pathways for airways diseases (AIRWAYS ICPs) has been chosen as the model of chronic diseases. Its goals are to launch a collaboration to develop multisectoral care pathways for chronic respiratory diseases in European countries and regions, and beyond with the Global Alliance against respiratory diseases (GARD). One of the major actions of AIRWAYS ICPs is to launch care pathways for chronic respiratory diseases, which can be applied at the national and regional levels in Europe.

ARIA (Allergic Rhinitis and its Impact on Asthma) represents the most widely used guideline for allergic rhinitis (AR) and asthma comorbidity. ARIA comprises a study group of 350 members and has been disseminated in over 65 countries to specialists, general practitioners, pharmacists, other health care professionals, social carers and, importantly, patients.

KEY MESSAGES

- ARIA (Allergic Rhinitis and its Impact on Asthma) represents the most widely used guideline for allergic rhinitis (AR) and asthma comorbidity
- The new ARIA strategy is to develop recommendations, which will be used globally and applicable to each individual region or country of Europe depending on the health system, the cultural barriers, the availability and reimbursement of treatments and diagnosis, patients and health care professionals views
- Active and Healthy Ageing is a major societal challenge common to all countries and populations
- Integrated care pathways for airways diseases (AIRWAYS ICPs) has been chosen as the model of chronic diseases by the European Innovation Partnerships
- One of the major actions of AIRWAYS ICPs is to launch care pathways for chronic respiratory diseases which can be applied at the national and regional levels in Europe

ARIA is disseminated in over 60 countries and has been translated into over 50 languages. Furthermore, it has been used in several guidelines recommended by governmental health agencies (e.g. Brazil Portugal, Singapore, and the Finnish Allergy Programme).

The importance of clinical guidelines is widely recognized, but confusion exists on terminologies used to describe various forms of evidence-based tools to inform clinical practice.

A best practice is a technique, method, process, activity, incentive, or reward that is believed to be more effective at delivering a particular outcome than any other technique, method, process, etc. when applied to a particular condition or circumstance. A best practice can be adopted as a standard process or be used as a guideline (U.S. Dept. of Veterans Affairs).

A **guideline** is a statement to determine a course of action. It aims to streamline particular process-

es according to a set routine or sound practice. By definition, following a guideline is never mandatory. Guidelines are not binding and are not enforced.

Clinical practice guidelines are systematically developed statements to assist the practitioner and patient decisions about appropriate health care for specific clinical circumstances. (Institute of Medicine, 1990). Clinical practice guidelines define the role of specific diagnostic and treatment modalities in the diagnosis and management of patients. The statements contain recommendations that are based on evidence derived from a rigorous systematic review and synthesis of the published medical literature. Clinical practice guidelines are not fixed protocols that must be followed, but are intended for health care professionals and providers to consider. While they identify and describe generally recommended courses of intervention, they are not presented as a substitute for the advice of a physician or other knowledgeable health care professional or provider.

The integrated care pathway (ICP) concept was initiated in 1985 by Zander and Bower. ICPs are structured multidisciplinary care plans which detail essential steps in the care of patients with a specific clinical problem. They promote the translation of guidelines into local protocols and their subsequent application to clinical practice. An ICP forms all or part of the clinical record, documents the care given, and facilitates the evaluation of outcomes for continuous quality improvement. ICPs can help empower patients and their carers (health and social). ICPs differ from clinical practice guidelines as they are utilized by a multidisciplinary team and have a focus on the quality and co-ordination of care. ICPs need to have a mechanism for recording variations/deviations from planned care. An ICP is intended to act as a guide to treatment. Clinicians are thus free to exercise their own professional judgments as appropriate. However, any alteration to the practice identified within this ICP must be noted as a variance. Variance analysis is a critical part of developing and using ICPs. The resulting analysis can be used to amend the ICP itself if, for the majority of patients, the practice is different to the pathway (Table 1).

The new ARIA strategy is to develop recommendations which will be used globally and applicable to each individual region or country of Europe depending on the health system, the cultural barriers, the availability and reimbursement of treatments and diagnosis, patients and health care professionals views. They will therefore represent the link between guidelines and care pathways.

The ARIA care pathway document will be launched during a meeting at the Ministry of Health of Portugal, July 1-2, 2015 organised by the Région Languedoc Roussillon, the Reference Site Network of the EIP on AHA and the Directorate General of Health of Portugal in collaboration with WHO GARD (Global Alliance against Chronic Respiratory Diseases). Scientific societies like EAACI will participate to this launch.

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TABLE 1

Definition of guidelines, practice protocols and ICPs *

	Guideline	Clinical Practice Guidelines	Integrated Care Pathway
Focus	Specific clinical circumstances (SPC)	Treatment and prevention	The quality and co-ordination of care.
Definition	Systematically developed statements to assist practitioners and patient make decisions about appropriate health care.	A suggested course of treatment and/or treatment service for a specific diagnosis, functional deficit or problem area.	Structured, multi-disciplinary plans of care.
Goals	Makes specific recommendations on health care and links these to research evidence.	Highlights major therapeutic intervention points. Identifies choices of difference courses or paths of treatment.	Supports the implementation of clinical guidelines and protocols.
Outputs	Provides a summary and appraisal of the best available research evidence or expert consensus. Highlights the strength of the evidence underlying each recommendation.	Provides a logical flow of interventions. Provides detailed recommendations that build on those made in SPCs guidelines.	Provides detailed guidance for each stage in the management of a patient.
Users	Clinicians, patients and third parties.	All stakeholders	A multidisciplinary clinical team.
Components	1) Appraisal of literature (research evidence or expert consensus). 2) Summary of recommendations. 3) An outline of how guideline should be implemented and how adherence monitored.	1) List of major interventions. 2) Goals: When interventions should be achieved. 3) Options for different choices of interventions.	1) Timeline 2) Categories of care/ intervention. 3) Intermediate and long term outcome criteria. 4) A variance record

* *Adapted from http://www.implementationcentral.com/guidelines_8.html, accessed May 27, 2015.*

3 SEVERE CHRONIC UPPER AIRWAY DISEASES

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KEY MESSAGES

- SCUAD is the acronym for Severe Chronic Upper Airway Diseases
- A great percentage of allergic rhinitis (AR) patients are not controlled and they need to use more then one or two drugs
- SCUAD is present in 10-20% of AR patients
- SCUADs have great impact for defining treatment for AR, including allergen immunotherapy

SCUAD is the acronym for Severe Chronic Upper Airway Diseases suggested by Bousquet et al. in 2009. Actually the title of the paper was really self explaining, since it was devoted to identify the unmet needs in this pathological condition. Among the different phenotypes of rhinitis, infectious and allergic rhinitis (AR) are those that are best characterized from a pathophysiologic point of view.

AR is sometimes considered a trivial disease and is neglected, although its economical burden is over 2000 € per patient per year. These costs should be multiplied by a remarkable number of patients, since the prevalence of AR is quite relevant, so the real socioeconomic burden of AR is even higher. In real life, the majority of patients had persistent symptoms (73%), and AR of moderate-severe degree (70%). The majority of patients with AR present with controlled symptoms during treatment, but many patients suffer from SCUAD. SCUAD defines those patients who remain uncontrolled despite adequate (i.e. effective, safe and acceptable) pharmacologic treatment based on guidelines (ARIA & EPOS). SCUAD accounts for 10-18% of AR patients ondergoing treatment.

It can be envisaged that the diagnostic/therapeutic approach is not supporting a correct treatment to AR patients, so they are worsening and developing a SCUAD. Patients may not understand the benefits from treatment and compliance to treatment is poor. A substantial proportion of such patients do not reach optimal pharmacological treatment.

SCUAD patients are likely to have impaired quality-of-life including social functioning, sleep, school and/or work performances.

Although quite a few patients with AR are not sufficiently controlled by current treatments in clinical practice, the prevalence of uncontrolled rhinitis and its impact on quality-of-life or work are unknown. In reality, patients with AR reach optimal health-related quality of life (HRQoL) in just one third of cases, mainly due to comorbid asthma, while unsatisfactory disease control was the primary reason why the individuals remaining from one third failed to attain optimal HRQoL.

Impacting limitations in daily life is reported for 45% of AR patients in a recent study in Italy, and 61% of AR patients are worried about possible unfavorable evolution of the disease. In real life, sadely, AR patients use automedications first, referring to the general practioner in a small percentage and of course even less to specialists. A recent survey conducted in Italy detected that the majority of AR patients use more then one single drug; 36% use two drugs; 13% three drugs and 6% more than three drugs. So, it is reasonable to suggest that quite a few SCUAD patients are

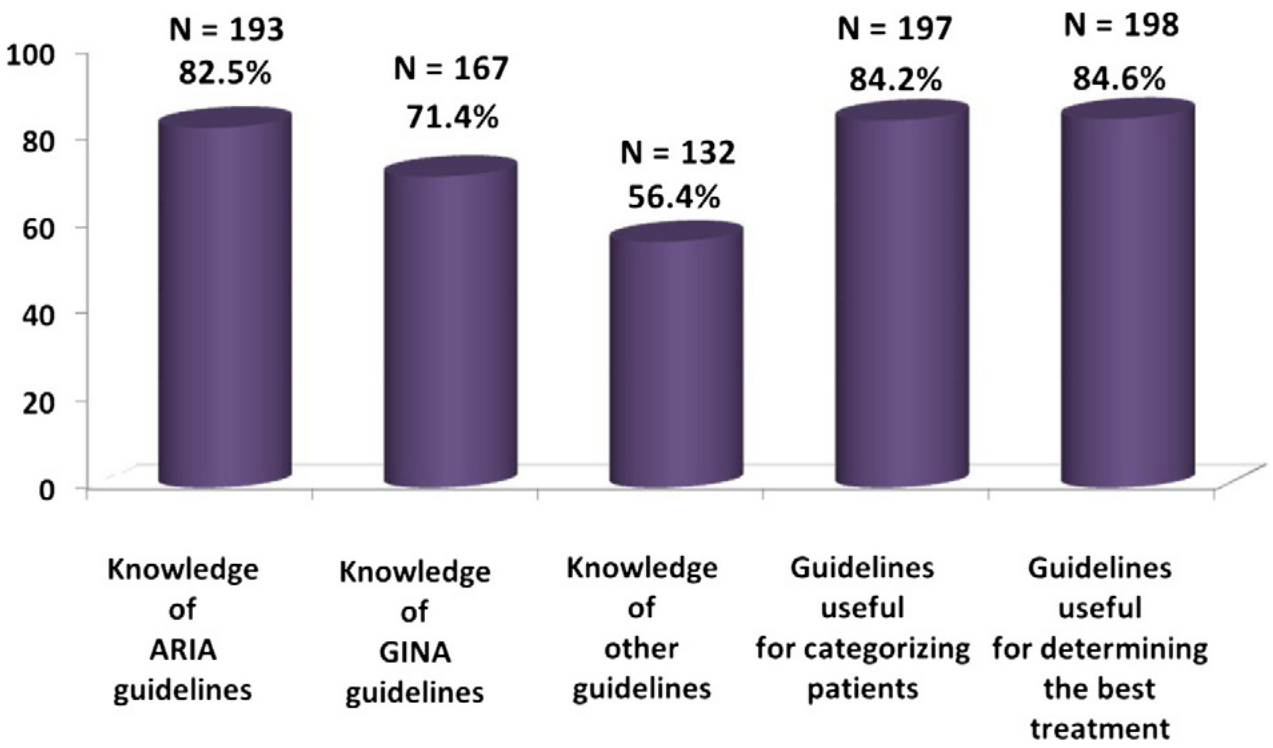

Figure 1 Use of guidelines reported by physicians [Number and percentage of physicians]. Physicians answered to the following question: Do you know ARIA, GINA or other guidelines? Do you find guidelines are useful in categorizing patients? Are guidelines useful to find the best treatment for your patients? (*Reproduced from Baena-Cagnani CE, Canonica GW, Zaky Helal M, et al. The international survey on the management of allergic rhinitis by physicians and patients (ISMAR). World Allergy Organ J 2015;8:10.)*

not even suspected or detected and that SCUAD is possibly underestimated in real life.

Recent data of the ISMAR study, performed in different parts of the world, suggested an extensive clinical use of guidelines (Figure 1).

However, it was recently demonstrated that although "ARIA in the Pharmacy" program was disseminated, just 13% of pharmacists, are aware of the ARIA Guidelines. This approach is not anymore structured in real life as it was proposed in the educational programs. New initiatives are needed, such as the Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc Roussillon (MACVIA-LR) programme.

Nonetheless, because of their severity and socioeconomic consequences, SCUADs need special attention to better define its prevalence and mechanisms. Priorities for research in SCUADs can be listed as: definition of genotypes/phenotypes in relation to disease heterogeneity, immune responses (innate and specific), and inflammation; assessment of prevalence, burden, and costs of different causes of SCUADs; assessment of SCUAD comorbidities; development of new forms of treatment; longitudinal evaluation of SCUADs to find preventive strategies.

Because of the economic impact, some Regulatory Bodies are restricting the reimbursement of Allergen immunotherapy (AIT) mainly to SCUAD. This is a further reason to promote phenotypic characterisation and stratification of allergic patients, characterisation of SCUAD patients and characterisation of AR patients to be treated by AIT. In this respect, three innovative tools (AIRWAYS-ICP, the allergy sentinel network and AIRWAYS-CDSS) will be combined in the MACVIA-ARIA Sentinel NetworK (MASK) and will make it possible to assess some of the unmet needs in research of AIT (Table 1).

The final remark should be consistent with the previous data on SCUADs, since because of their severity and socioeconomic consequences, SCUADs need special

TABLE 1

MASK innovative goals
Assessment of prevalence and severity of allergic diseases.
Phenotypic characterisation of allergic patients, stratification of patients, characterisation of SCUAD patients and characterisation of patients to be treated by AIT.
Randomised controlled trials (placebo-controlled or real life cluster randomised trials): assessment of efficacy (during the allergen exposure) and the safety (during AIT administration)
Follow up of patients in clinical settings during AIT
Follow up of patients in clinical settings after AIT has been stopped.

attention in daily clinical practice and in research to better define their prevalence, risk factors, severity, mechanisms and novel treatments.

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4 IMPORTANT RESEARCH QUESTIONS IN CHRONIC UPPER AIRWAYS DISEASES

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State-of-the-art documents like Allergic Rhinitis and its Impact on Asthma (ARIA) and the European Position Paper on Rhinosinusitus and Nasal Polyps (EPOS) provide clinicians with evidence-based treatment algorithms for allergic rhinitis (AR) and chronic rhinosinusitis (CRS). However, a significant number of patients with AR and CRS continue to experience bothersome symptoms despite adequate treatment. This group, the so-called severe chronic upper airway disease (SCUAD) represents a continuous therapeutic challenge. Further research regarding the diagnostic, therapeutic and patient-related factors that are responsible for uncontrolled upper airway diseases are needed.

Allergen immunotherapy (AIT) is already an available causal treatment for AR. Subcutaneous immunotherapy (SCIT) is in most cases effective in the short term (3-4 years). However, its long-term efficacy is still unclear. Recent data indicate that sublingual immunotherapy (SLIT) is an effective treatment modality for seasonal AR but head-to-head studies comparing SLIT to SCIT are needed. SCIT and SLIT are both safe and effective treatments for AR, but strict compliance is crucial to achieve good clinical effects. There is, consequently, a need for further identification of potential obstacles and of measures that will enhance a better compliance in AIT.

Non-allergic rhinitis (NAR) can be defined as chronic nasal symptoms that are not caused by IgE-dependent mechanisms or related to structural anomalies. Several causes include hormonal imbalance, physical/chemical agents, psychological factors, air pollution and certain drugs. Taking into account the heterogeneity of NAR there is a need for better understanding of the pathophysiology of the disease and its risk factors,

KEY MESSAGES

- Further research regarding the diagnostic, therapeutic and patient-related factors that are responsible for uncontrolled upper airway diseases are needed
- Endotypes and phenotypes of AR and CRS should be established with a consensus after better understanding of their mechanisms
- Evidence for the long-term effect for subcutaneous allergen immunotherapy (SCIT) are lacking as well as a head-to-head studies comparing SCIT to sublingual allergen immunotherapy (SLIT)
- There is need for further identification of potential obstacles and of measures that will enhance a better compliance for allergen immunotherapy
- Early biomarkers for SCUAD development, therapy responses in AR and CRS and patient selection for AIT are needed
- For non-allergic rhinitis (NAR) there is a need for better understanding of its pathophysiology and risk factors, as NAR is a heterogeneous disease
- For chronic rhinosinusitis with and without nasal polyps, there is a further need for larger randomised placebo-controlled trials investigating the effect of existing and novel medical therapy

to guide us toward an improved diagnosis and therapy.

Local allergic rhinitis (LAR) is characterized by the presence of a nasal Th2 inflammatory response with local production of specific IgE antibodies and a positive response to a nasal allergen provocation test without evidence of systemic atopy. According to one report the prevalence of LAR tends to be up to 25% in subjects affected with persistent rhinitis presenting a comorbidity and the clinical pattern similar to AR. The real prevalence of LAR in the general population remains, however, unknown and is probably overestimated.

With regard to chronic rhinosinusitis (CRS) with and without nasal polyps, there is a further need for larger randomised placebo-controlled trials investigating the effect of existing and novel medical therapy. A better understanding of the pathogenesis and factors enhancing mucosal inflammation is crucial for the development of new diagnostic and therapeutic tools. The main objective for future research should be the identification of clinical parameters, infectious agents, inflammatory mechanisms and remodelling processes in patients with upper airway disease, so that those patients can be categorized into clinically relevant subgroups based on clinical phenotyping and biomarker profiles. Defining and predicting response to therapy in individual CRS patients is a challenge for future research.

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5 POLICIES AND STRATEGIES TO FACILITATE ACCESS TO DIAGNOSIS AND TREATMENT FOR CHRONIC UPPER AIRWAY DISEASES

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KEY MESSAGES

- More responsibility of upper airways´ allergy care is shifting to primary care. The Primary Care Physicians need organized education to improve their skills for the diagnostics and management of rhinoconjunctivitis and rhinosinusitis
- Allergy testing centers should be formed in public health care to serve all practitioners in the region. This is for better quality of the testing itself as well as for proper result interpretation
- National or regional Allergy Plans are recommended to improve the care of multifaceted allergic conditions. Local groups of experts and stakeholders decide the division of labour, supervise the management processes and follow up results as well as costs

PRACTITIONER LEVEL

The vast majority of all allergy patients are managed by the general practitioners (GP) (or general allergists) in the outpatient care. This work is supplemented by ENT-specialist -, and hospital based care, if extensive rhinoscopic examinations, CT-scan or surgery are needed. Every GP or general allergist should have the equipment to perform simple anterior rhinoscopy as well as otoscopy. The GPs should detect severe mucosal inflammation, infectious secretion, polyposis, obvious tumors and marked anatomical changes like septum deviation. The GPs should have an easy access to x-rays or ultrasound examination to diagnose sinusitis and mucosal swelling. Many GPs are also able to drain maxillary sinuses.

Management of allergic upper airways conditions is not taking place in a vacuum. If the patient is atopic, often lung -, skin -, and sometimes gastrointestinal symptoms co-exist. These co-morbidities need attention to control the common inflammatory condition (Table 1).

SOCIETAL LEVEL

There is no straightforward trend of worsening in allergy; mild symptoms often improve, even without treatment. For mild rhinoconjunctivitis, guided self-management and follow-up are generally sufficient. Extensive diagnostic examinations should be performed if the symptoms continue, become more severe and cause disability or marked inconvenience.

TABLE 1

How to improve the management of rhinitis and asthma	
Allergic rhinitis is treated better	Ask asthma symptoms in every rhinitis patient.
	Measure lung function (PEF, spirometry) in chronic rhinitis patients
	Look at the eye conjunctiva
	Look at the skin
	Guide the patient to self-management “Rhinitis Control Card” etc.
Asthma is treated better	Ask rhinitis symptoms in every asthma patient

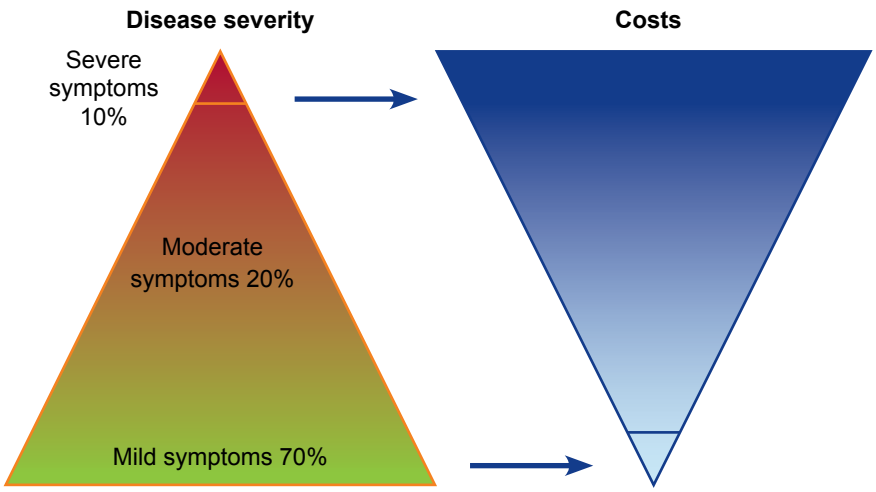

Figure 1 The schematic allergy pyramid. Most of the allergy symptoms are mild or intermittent, but due to high prevalence, severe symptoms are also common and cause majority of the costs.

Because of the high occurrence of allergies in the urbanized world, even the number of patients with severe upper airway symptoms is high, and the healthcare system should allocate resources to manage them. Severe symptoms cause the majority of costs, which can be considerably reduced by preventive and good symptom control (Figure 1).

Diagnostic allergy practices vary greatly between countries and even in the same country. The GPs should be able to refer their patients to simple skin prick testing to common allergens. The test answers to two basic questions: 1) does the patient have an atopic disposition (any positive, at least 3 mm wheal reaction), 2) is there a causal relationship of any of the tested allergen and current symptoms?

In the Finnish Allergy Programme 2008-2018 public health allergy testing is centralized to large hospitals, which give testing service to the whole region, also to GPs. This strategy has considerably improved the quality of testing and interpretation of results. Diagnosing the upper airway allergies needs precision and both under- and over-diagnostics should be watched. The former causes unnecessary suffering and the latter overuse of drugs.

As improving immune tolerance is increasingly emphasized in modern allergy treatment, the patients should have a better access to allergen immunotherapy (AIT). This is now feasible when AIT injections are more and more turning to sublingual immunotherapy (SLIT) with tablets and drops. An allergy trained GP should be able to start SLIT and follow it up.

It is crucial that the management chains and processes are regionally thought over, written down and organized between GPs, allergy testing centers and specialist care units. Basically: who is doing what and when? **A national or regional "Allergy Plan"** is very useful in facilitating comprehensive allergy care and co-operation between different healthcare units with the aim of better management and less costs.

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6 POLICIES AND STRATEGIES TO REDUCE RISK FACTORS FOR ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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Many risk factors are known to be associated with manifestations of allergic conditions including allergic rhinitis (AR) and asthma. However, the exact roles of these factors in the inception of AR and chronic rhinosinusitis (CRS) are not clear. The rapid increase of AR with urbanization clearly suggests the importance of environmental factors in the development of AR. The implicated factors include indoor and outdoor allergen exposure, environmental air pollutants including tobacco smoke exposure, and indoor humidity (Figure 1). The most important predisposing factor for rhinosinusitis is AR and adequate treatment of AR will reduce the burden of rhinosinusitis. Effective implementation of public policies regarding pollution, building codes, city planning and planting practices many help to reduce the burden of AR and CRS.

KEY MESSAGES

- Many factors are known to be associated with the development of allergic rhinitis (AR) and chronic rhinosinusitis in genetically predisposed individuals and these factors can be controlled by implementation of effective public policies
- Public policies in controlling outdoor environmental pollution, reducing environmental tobacco smoke exposure and implementation of building codes may reduce the related environmental risk
- Global warming is likely to affect the environmental composition and distribution of pollen allergens resulting in possible increase in AR
- Proper environmental control in the workplace can limit occupational exposure thereby reducing morbidity associated with occupational rhinitis

OUTDOOR ENVIRONMENT

Many outdoor environmental pollutants, including ozone, nitrogen dioxide, sulfur dioxide, and particulate matter, can induce sino-nasal mucosal irritation and inflammation. Much of these pollutants are generated from burning of biomass fuels and exhausts of motor vehicles. There were many animal

Figure 1 The complex interplay between the outdoor and indoor environment.

TABLE 1

European Ambient Air Quality Standards *		
Pollutant	**Concentration (µg/m³)**	**Averaging period**
Fine articles (PM2.5)	25	1 year
Sulphur dioxide (SO_2)	350	1 hour
	125	24 hours
Nitrogen dioxide (NO_2)	200	1 hour
	40	1 year
PM10	50	24 hours
	40	1 year
Carbon monoxide (CO)	10	Maximum daily 8 hour mean
Ozone	120	Maximum daily 8 hour mean

** From European Commission Ambient Air Quality Standards. http://ec.europa.eu/environment/air/quality/standards.htm, accessed May 20, 2015.*

studies confirming the detrimental effects of environmental pollutants on the nasal mucosa. Human studies corroborated the experimental findings documenting the association of outdoor ozone concentration and leucocytes in nasal secretions in a dose-dependent manner. Exposure to particular matter related to diesel exposure has been shown to increase upper airway expression of inflammatory cytokines. As there are no clear-cut thresholds of safety level for various pollutants in relation to airway diseases, public policies should aim to reduce these pollutants to the lowest possible levels (Table 1).

Exposure to pollen is another major risk factor for the development of AR. Due the increasing demand for green space in modern cities careful consideration during urban planning is needed for the selection of plant species thereby minimizing aeroallergen concentration. Due to the phenomenon of global warming, the distribution and dispersion of various grass or tree related pollens are likely to change and may result in increase of AR across the world. Detailed environmental monitoring will be needed to document the effects of global warming.

INDOOR ENVIRONMENT

Environmental tobacco smoke (ETS) can damage the sino-nasal mucosa by local irritation and immune-related effects. In human studies, exposure to ETS has been found to be associated with increased prevalence of CRS. Active smoking has also been shown to increase the personal risk of developing chronic rhinitis. Public policies in reducing secondhand tobacco smoke exposure will likely to be associated with benefits in subjects prone to develop chronic rhinitis.

Indoor environmental allergens, including house dust mites, pet allergens, and mold allergens, have been widely implicated to be the major factors associated with AR. Poor ventilation and excessive humidity in households result in excessive growth of indoor molds and house dust mites thereby affecting susceptible individuals. Public policies governing building codes and control of indoor humidity are likely to be translated into health benefits with reduction of morbidity due to AR.

OCCUPATIONAL EXPOSURE

Occupational rhinitis refers to symptoms of the upper airways due to exposure to irritants or allergens at the workplace. Although it is not as well characterized as occupational asthma, it is more likely to be underdiagnosed and more research is needed in the area. The implicated occupational agents are usually classified as low (<5 kDa) or high (>5 kDa) molecular weight agents (HMW or LMW). HMW agents refer to biological substance such as latex, laboratory animals, or flour. LMW agents are usually synthetic chemicals such as those found in hair bleachings, epoxy resins, or drugs which can act as immune sensitizer. Symptoms typically would improve during holidays but get worse upon return to work.

Public policies in setting standards at work places aiming to reduce exposure to the related occupational agents will help in the primary and secondary prevention of work related AR.

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7 THE ROLE OF PRIMARY HEALTH CARE IN THE MANAGEMENT OF CHRONIC UPPER AIRWAY DISEASES

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KEY MESSAGES

- Chronic upper airways disease are a common problem in primary care
- The history is the key to diagnosis
- A holistic, patient centered approach is advocated
- Specialist referral is indicated for persistent or uncontrolled symptoms

Chronic upper airway disease (Table 1) is an umbrella term covering a multitude of potential problems, the most common of which are allergic in nature, but which may co-exist with and exacerbate or be exacerbated by another disorder.

In the general population rhinitis is frequently under recognised and managed sub optimally. The pharmacist is often the first person an individual encounters when seeking alleviation from the symptoms of chronic upper airways problems, the most common varieties of which are persistent allergic and non - allergic rhinitis. Over the counter remedies commonly available include saline nasal douches, nasal decongestants, topical nasal steroids and antihistamines, but this varies from country to country. It is strongly recommended that first generation antihistamines are no longer used because of their adverse side effects.

TABLE 1

Chronic Upper Airway Disease
Allergic rhinitis
Nonallergic rhinitis
Chronic rhinosinusitis
Aspirin exacerbated respiratory diseases
Occupational airway diseases

Should the patient not respond, it is suggested that he is signposted to his general practioner (GP). Mild allergic rhinitis (AR) is usually managed at pharmacy level the result of which is that the majority of those presenting in primary care have moderate or severe disease (Figure 1). In all instances of airways disease, it is wise to enquire about the presence of lower airways symptoms and in particular asthma

A major confounding factor is the presence of non AR, which has a number of aetiologies, on which treatment success relies on identification and removal of the aetiological agent (Figure 2).

The role of the GP is thus to take a comprehensive, allergy focused clinical history, which will include seeking a history of precipitating, exacerbating and relieving factors, any co-morbidities, in particular asthma and any medications which have been tried as well as prescriptions for other problems such as hypertension, contraception or pain relief; this will be accompanied by a relevant physical examination in particular searching for signs of remediable problems such as deviated nasal septum and polyps, which may point to salicylate sensitivity.

In all instances, exposure to cigarette smoke is deleterious and cessation advice should be offered. Having made as precise a diagnosis as possible a management plan will be drawn up informed by relevant guidelines. It is important to recognize that AR and non AR may co exist. The majority of patients can be managed in primary

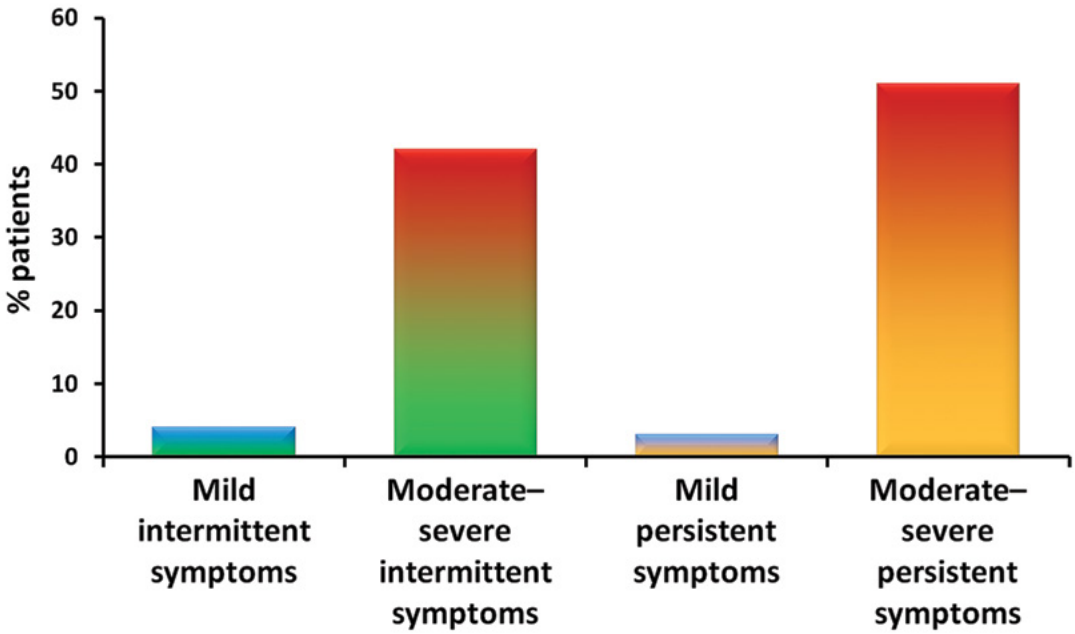

Figure 1 Symptom severity profiles of those presenting with allergic rhinitis to primary care.

SYMPTOMS SUGGESTIVE OF ALLERGIC RHINITIS	SYMPTOMS USUALLY NOT ASSOCIATED WITH ALLERGIC RHINITIS
2 or more of the following symptoms for >1hr on most days • Watery anterior rhinorrhea • Sneezing (esp. paroxysmal • Nasal pruritis • ± conjunctivitis	• Unilateral symptoms • Isolated nasal obstruction without other symptoms • Muco-purulent rhinorrhea • Posterior nasal drip • Pain • Recurrent Epistaxis • Anosmia

Figure 2 Criteria for separating allergic rhinitis from non-allergic rhinitis in primary care.

care (PC). Blood tests (specific IgE) or skin prick tests, guided by an appropriate clinical history can be helpful in determining management for those with poorly controlled or persistent symptoms. Results should be interpreted in the context of the clinical history. Patient centered care, with shared decision making about the different treatment options, after exploring the patient's ideas concerns and expectations is encouraged to ensure good compliance and improve outcomes. Treatment should ideally be tailored to individual needs.

The presence of facial pain or pressure, reduction or loss of sense of smell accompanied by symptoms of nasal obstruction or blockage should lead the clinician to consider the diagnosis of rhinosinusitis. This is conveniently sub categorized into acute, for episodes which completely resolve,

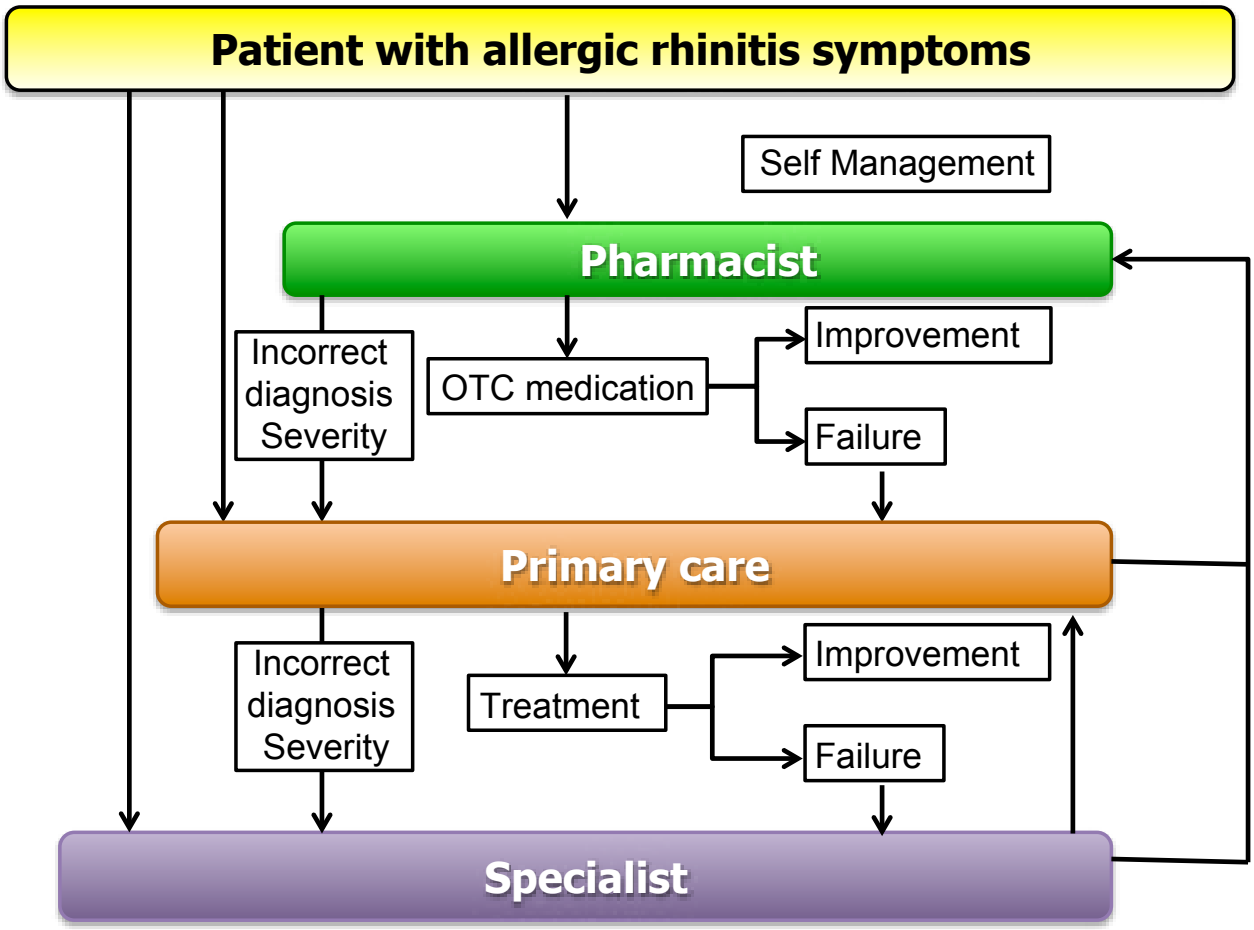

Figure 3 Integrated care pathway for allergic rhinitis.

and chronic, for periods of greater than 12 weeks or in which complete resolution has not occurred. Chronic rhinosinusitis (CRS) may be subcategorized as with or without polyps. Treatment options are best determined following specialist consultation. A full exploration of the approach to management of CRS is offered by the European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS) 2012.

It is likely that future models of care will implement management strategies with the patient at the center of any management pathway facilitating the escalation of care to those with greater levels of expertise and resources needed, within an appropriate time frame if symptoms are failing to come under control (Figure 3).

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8 THE ROLE OF PATIENT ORGANISATIONS IN THE MANAGEMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

EAACI Patient Organisation Committee

KEY MESSAGES

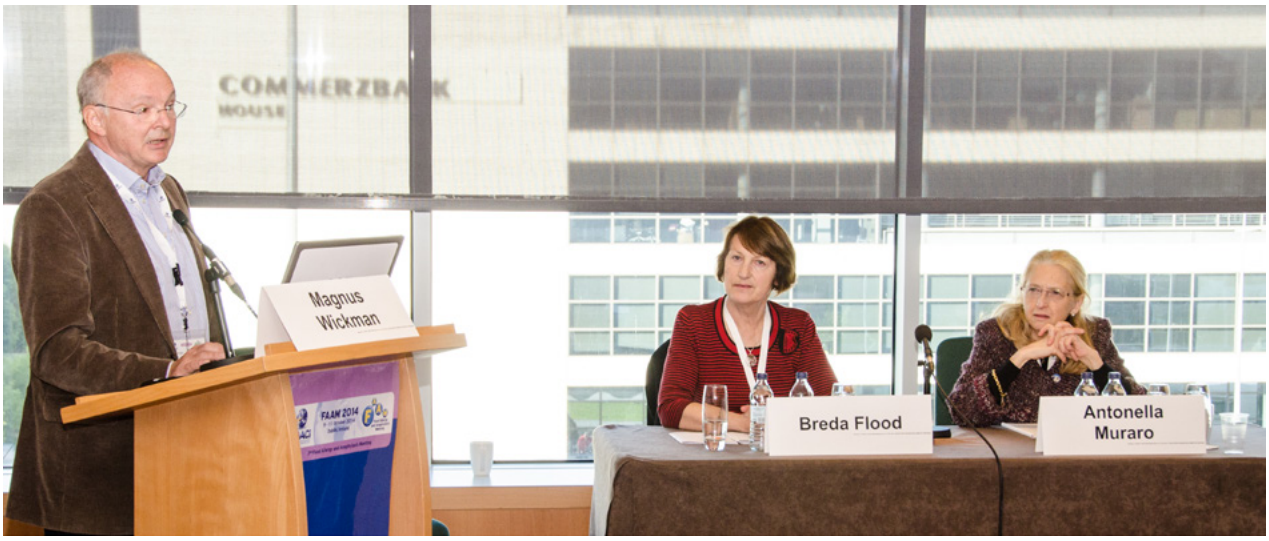
- Unacceptable of reduction of quality of life should not be tolerated, there are several solutions for improvement
- Patient organisations traditionally provide peer support, information and education for patients and their carers to cope with their disease
- The EAACI Patient Organisation Committee offers a well-organised and sustainable platform for communication and dissemination of guidelines and other key recommendations and educational programmes, enabling mutually beneficial interactions between patients and clinicians
- Patient organisations revolutionised advocacy and the political influence of patient organisations grows as they strive for action and change, with the inclusion of patient representatives in official bodies advising on health, care and research policies
- Education and a patient-centered attitude are key steps towards a better management of allergic diseases

Patient organisations provide traditionally peer support, information and education for patients to support their journey through the health care system. Patient organisations aim to promote practical prevention and improve the quality of life (QoL) for people affected by health conditions and for their families, through patient participation and empowerment.

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) affect millions of people in Europe, and billions in the world, in their QoL, without them realising it. Not only the general public but also patients perceive "hay fever" as something that causes minor disruptions and bearable complaints, and the ones who suffer from this disease mostly accept the reduction in quality of life due to AR and CRS. It is perceived as something that just belongs to life and we cope with the discomfort. In general the patient and the general public are not aware that they can live life to the fullest, just by treating the disease and managing its triggers.

These chronic inflammatory diseases of the upper airways do have a significant impact on the individual, the family and work. On a societal level the impact lies in the loss of workdays due to absence and loss of work effectiveness, thus generating a significant economic burden of annually more than several billions of Euros on employers and disease-related health care. The mean total productivity (absenteeism + presenteeism) losses per employee per year were 540 Euro for allergic rhinitis, 165 Euro for respiratory infections, The mean total productivity loss per employee per year due to caregiving was 93 Euro for pediatric respiratory infections.

Patient organisations within the EAACI Patient Organisation Committee (POC) platform are well equipped to assist clinicians in developing strategies in addressing issues to change policies on a national and European political level. The POC can make itself strong in bringing the unrecognised and hidden allergic burden into the political and societal spotlight to raise awareness and initiate actions with the ultimate goal to relieve the societal economic burden and foremost to raise the QoL



of patients with AR and/or CRS and other airway diseases.

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EAACI PATIENT ORGANISATIONS COMMITTEE

aha! Center for Allergy Switzerland

Allergy India

Allergy New Zealand Inc

Anaphylaxis Australia Inc

Anaphylaxis Canada

Anaphylaxis Ireland

Anoiksi NGO

Asociacion espanola de alergicos a alimentos y latex

Association Francaise pour la Prevention des Allergie (AFPRAL)

Association québécoise des allergies alimentaires

Astma-Allergi Danmark

Deutscher Allergie und Asthmabund eV

European Federation of Allergy & Airway Diseases Patients Association

Food Allergy Italia

Food Allergy Research & Education

Fundacion Creciendo con Alergias Alimenarias

Prevention des Allergies A.S.B.L.

S.O.S Alergia

Swedish Asthma and Allergy Association

The Allergy Society of South Africa

The Anaphylaxis Campaign UK

The European Anaphylaxis Taskforce CV

The Hong Kong Allergy Association

Yahel Food Allergy Network Israel

9 COMPREHENSIVE MANAGEMENT PLAN IN ALLERGIC RHINITIS – TOWARDS A PATIENT-CENTERED ATTITUDE

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KEY MESSAGES

- Patient organizations are non-profit organizations that represent centres of excellence in the allergy field
- The services they offer range from advising individuals and training courses, providing information, organizing self help groups through to prevention projects and campaigns for the population at large
- Most patient organizations work on the assumption that allergy sufferers are self-empowering and take responsibility for themselves
- Patient-centered measures are to be promoted to succesfully tackle the allergy epidemic

ALLERGY PATIENT ORGANIZATIONS

Patient organizations like aha! Swiss Allergy Centre are mostly non-profit organizations that represent centres of excellence in the allergy field. They focus on the reactions of the airways, digestive system and skin to environmental allergens and irritants, thus also on allergic rhinitis (AR). For the sake of creating awareness and take allergy preventive messages to the population, they seek visible public presence. Patient organizations are independent contact points for allergy sufferers and carers, but also for other interested groups such as the media, companies, training centres, politics, authorities and associations. The services they offer range from advising individuals and training courses, providing information, organizing self help groups through to prevention projects and campaigns for the population at large. These offerings are often made possible by widespread national and international networks and close co-operations with leading experts and professional bodies in the relevant spheres. Most patient organizations work on the assumption that allergy sufferers are self-empowering and take responsibility for themselves.

AIMS

Patient organizations want allergy sufferers and their families to have access to relevant, up-to-date and sound knowledge at the time and in the complexity, depth and form they need it in their respective situation. Sufferers shall have the skills, life circumstances and support they need to live their lives as symptom-free as possible and with a consistently high quality of life. The stakeholders in society shall take on their share of responsibility for the health-related living conditions and quality of life of all humans.

SERVICES

To achieve these aims, patient organizations offer sufferers, carers and other groups very well established services in the field of respiratory allergies and AR which are listed below.

- Expert advice. The main topics in connection with rhinitis discussed in those advices are listed in Figure 1.
- Interdisciplinary training courses and camps for children and adolescents. Children spend one week in summer or winter camps such as the one in Davos. They are regularly instructed in therapeutic measures and for example daily skin care and get answers to everyday questions concerning their allergies. The aim for the chil-

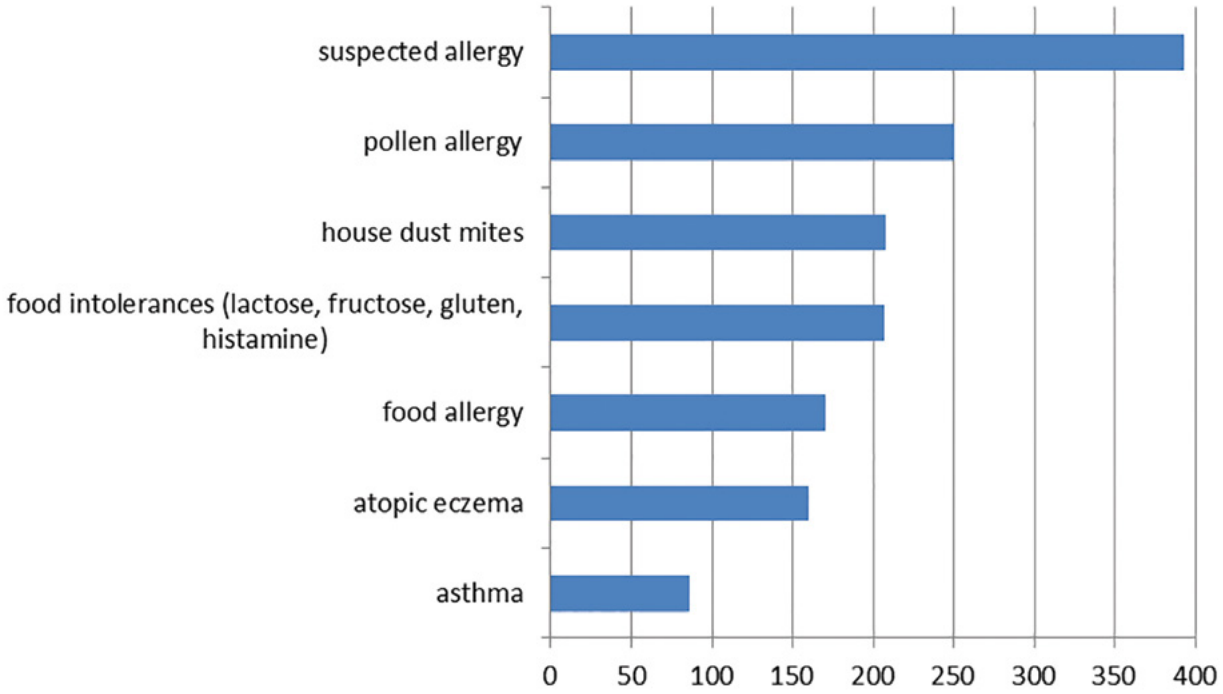

Figure 1 expert advices with indicated number of phone calls and e-mails in 2014.

dren is to have quality time in the mountains and meet other children, always with respect to their individual therapy and special needs in food. Continuous evaluation and quality assurance measures illustrate the effectiveness of those services: they clearly show the positive effect of the kids camp on independence and cooperation of participating children in the view of their parents.

- Publication of daily updates of pollen forecasts (14 pollen types) and pollen measurements (including weekly news alert) in close collaboration with the Federal Office of Meteorology and Climatology MeteoSwiss: Over 310'000 visitors on www.pollenundallergie.ch per year
- Smartphone applications for pollen forecasts, asthma control and documentation of allergic rhinitis and related trigger factors including studies about effectiveness of self monitoring
- Prevention and information campaigns on current topics
- Technical presentations on current topics
- Information about the variety of products and services which are suitable for allergy sufferers
- high-quality documentation, publications and information about respiratory allergies

Therewith, patient organizations support the health and quality of life of allergy sufferers, their families and potential sufferers and promote preventive action by a wide diversity of players. They campaign for high-quality, broadly accessible services such as primary prevention, with focus on living conditions and lifestyle and secondary prevention by improving patients and career skills. Aided by modern quality development, they strive for best professional practice.

TOWARDS A PATIENT-CENTERED ATTITUDE

In a global perspective, the number of sufferers from AR steadily increases. The diversity of known allergic diseases and allergens increases. At the same time, there is growing evidence that personalized measures are key for successful prevention and therapy of allergies. In parallel to this, it is increasingly difficult to raise funds for patient organization activities. Today, allergy patient organizations are heavily challenged by these facts. By choosing the ideal mixture of mass media communication (online and print), smartphone applications and individual advising on a one-to-one or one-to-few basis, this challenge has to be and will be mastered efficiently. In addition, online-based self-monitoring tools and personalized website surfaces can support patient-centered measures against the AR epidemic (Figure 2).

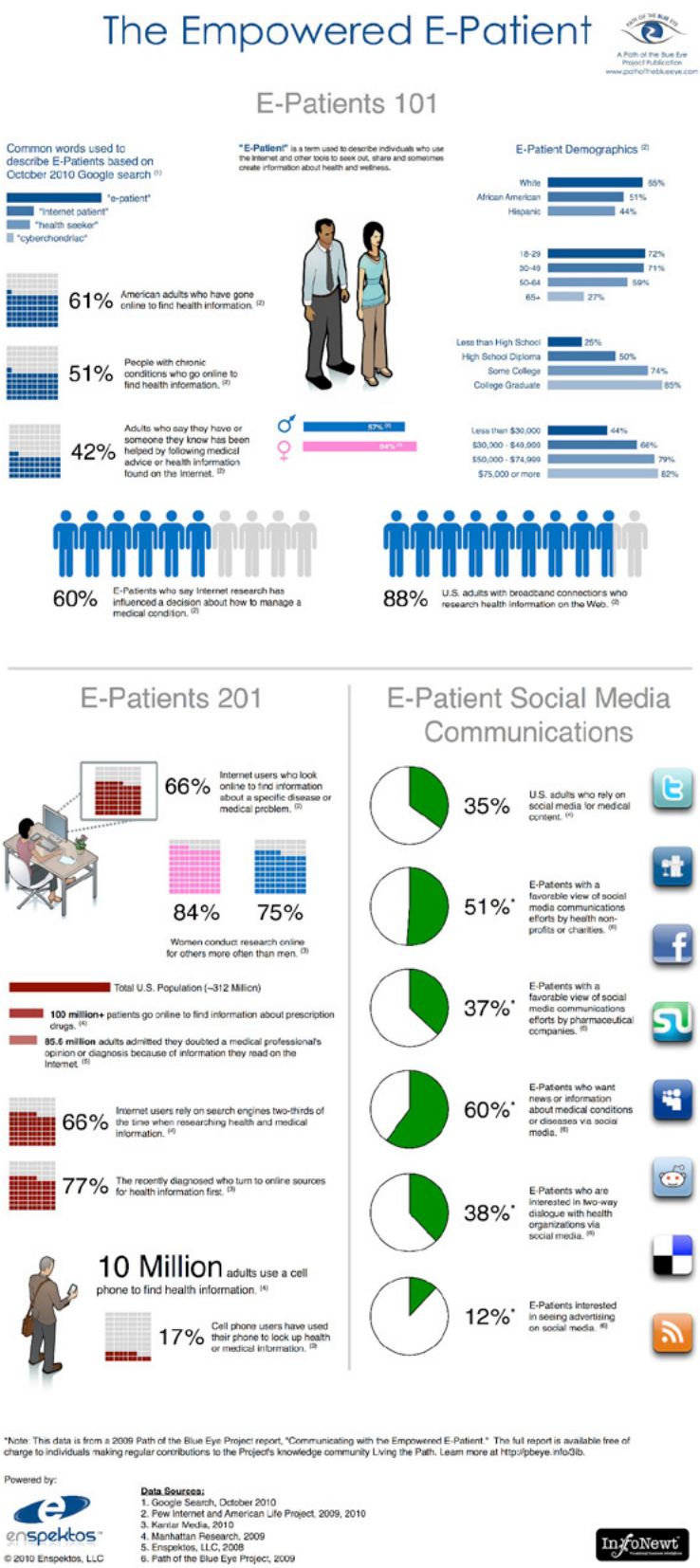

Figure 2 Health 2.0 and the patient centered attitude.

10 THE ROLE OF PHARMACISTS IN THE MANAGEMENT OF CHRONIC UPPER AIRWAY DISEASES

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Rhinitis is a highly diverse chronic disease spanning from mild intermittent rhinitis to chronic rhino-sinusitis with polyps and severe chronic upper airway disease (SCUAD). Multidisciplinary integrated care is necessary to reduce the burden of chronic diseases. A significant proportion of patients with rhinitis self-manage the condition and often the pharmacist is the first healthcare professional that a person with nasal complains contacts. Pharmacists are trusted in the community and are easy to access. As such, pharmacists are an important part of the multidisciplinary healthcare team acting at different steps of rhinitis care pathways.

Pharmacists are important in many areas of intervention in allergic rhinitis (AR):

1) Recognizing (identification)
2) Risk assessment/stratification
3) Over-the-counter treatment
4) Patient education
5) Referral to a physician
6) Teaching the technique for topical treatment and ensuring adherence to treatment

A good awareness of the pharmacist for recognizing AR and its main co-morbidities is mandatory to offer to the patient stratification of risk severity, and co-morbities assessment (e.g. asthma).

Simple algorithms and tools are essential to routine implementation of these steps. Standardized and validated tools are available to assess the diagnosis of AR, to recognize an urgent medical referral (eg unilateral bleeding), to assess rhinitis severity, impact on the patient's quality of life and control (Figure 1). A simple visual analogue scale (VAS) on the bothersome of nasal symptoms has been shown to be a sensitive tool for quantitative evaluation of severity of AR. VAS is highly responsive to change during treatment and very quick to complete, making it ideal for daily or frequent monitoring of AR. In addition The Control of Allergic Rhinitis and Asthma Test (CARAT) can help identify patients with uncontrolled rhinitis and/or asthma in pharmacy settings. These and other tools can help pharmacists to give optimal advice for patients with rhinitis. This advice can be over-the-counter treatment, topical treatment technique or referral to a physician, based on simple decision making algorithms (Figure 2).

Initiatives such as MACVIA–LR (Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc-Roussillon; Fighting Chronic Diseases for Active and Healthy Ageing)-ARIA (Allergic Rhinitis and its Impact on Asthma) in the pharmacy will help pharmacists to implement good practices contributing to a community-based integrated care of patients with AR.

KEY MESSAGES

- Pharmacists are trusted health professionals
- Many patients with allergic rhinitis (AR) are seen by pharmacists
- Pharmacists are able to identify, counsel and refer to a physician patients with AR
- The role of pharmacists in integrated care pathways for allergic diseases is essential

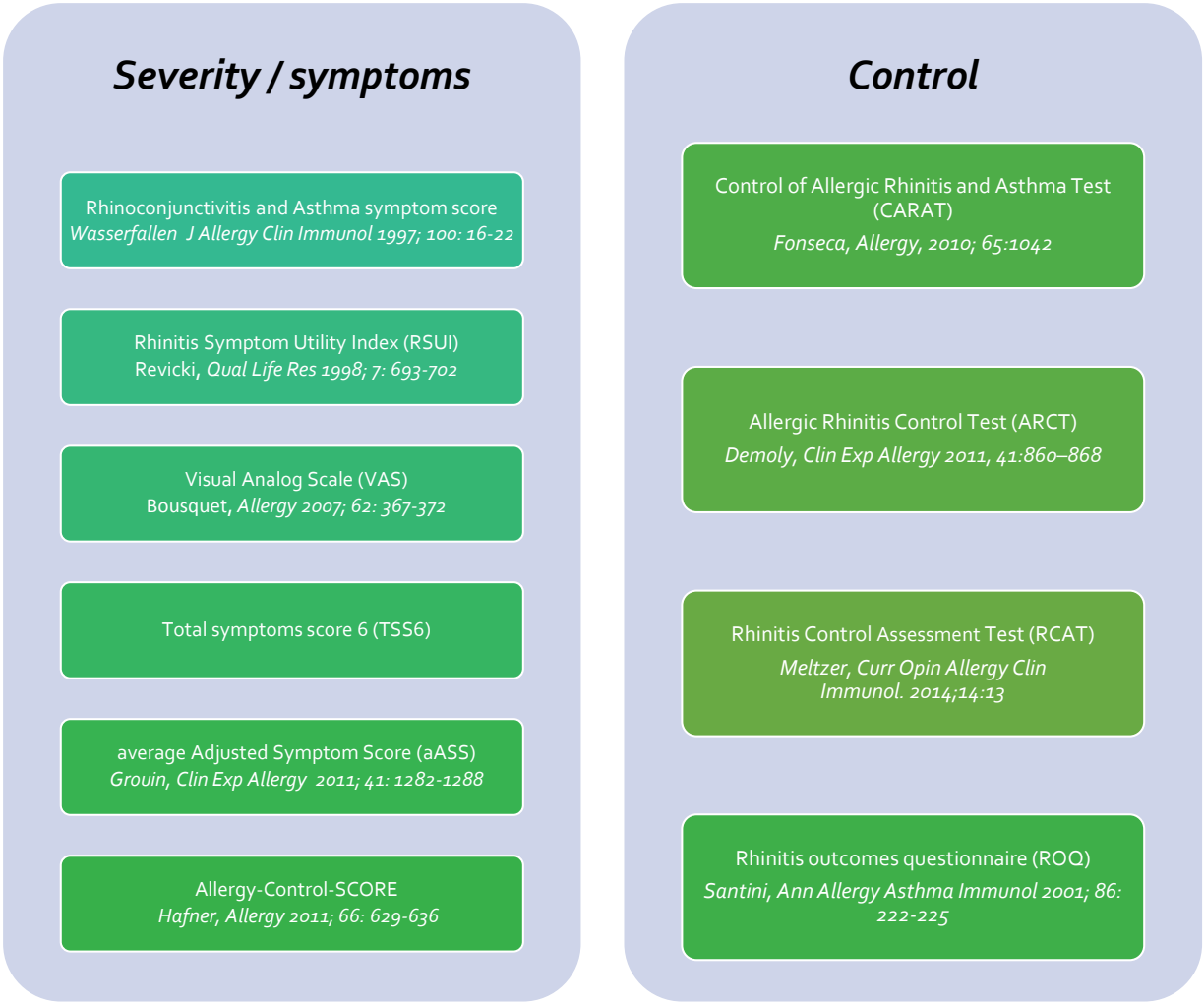

Figure 1 Instruments to assess of severity, symptoms and control and in allergic rhinitis and rhinosinusitis.

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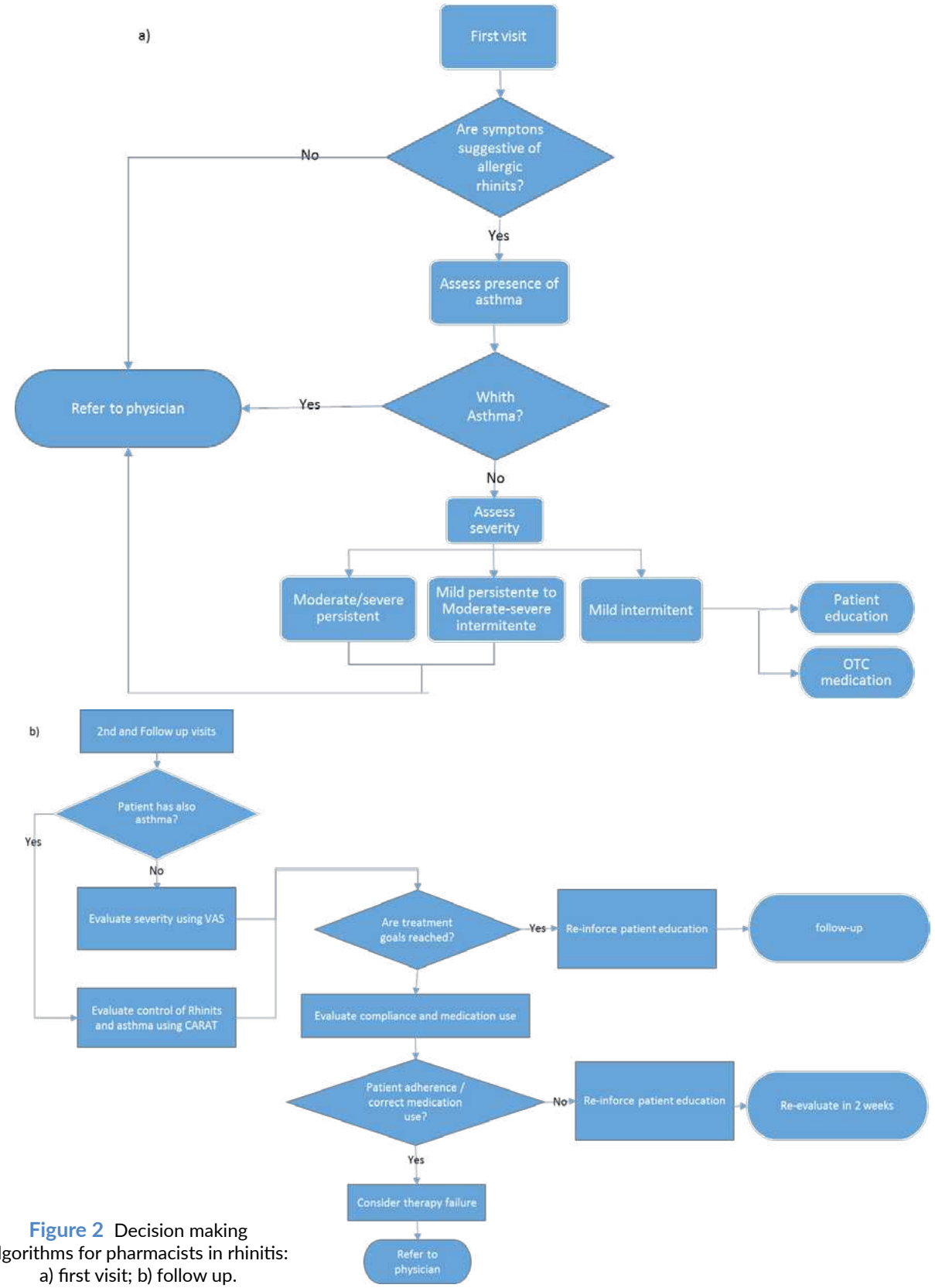

Figure 2 Decision making algorithms for pharmacists in rhinitis: a) first visit; b) follow up.

11 THE ROLE OF SCHOOLS IN THE MANAGEMENT OF CHRONIC UPPER AIRWAY DISEASE

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Allergic rhinitis (AR), the most prevalent chronic allergic disease in children, and chronic rhinosinusitis (CRS) can have considerable negative impact on children. They both affect children's quality of life, cognitive function, learning ability and the decision making process, thus resulting in significant impairment of the school performance (presenteeism). Under-diagnosed or untreated AR often exacerbates comorbid asthma and also causes school absenteeism or presenteeism.

Children spend most of their time in schools. Indoor and outdoor air quality is important, especially in children with vulnerable airways. Exposure to indoor allergens, such as house-dust mite, cat, dog, cockroach, fungi and mould can trigger symptoms in sensitized children with AR. Exposure to various indoor pollutants at schools, such as volatile organic compounds (VOC), depending on the use of marker boards, to cleansing or disinfecting chemicals for the classroom cleaning, and to particulate matter (PM) from chalk and dust may deteriorate airway disease. Additionally, poor indoor ventilation with exposure to high levels of CO_2 can reduce concentration ability of children.

KEY MESSAGES

- Students with chronic upper airway disease and comorbid diseases should be identified and recorded as part of the registration process in school
- Students with chronic upper airway disease are encouraged to have their medications readily available and safely stored at all time
- School staff should be knowledgeable about allergic rhinitis and its comorbidities, and should be able to handle worsening symptoms
- Good indoor air quality in the school must be provided by reducing indoor air pollutant sources, including allergens, and by improving indoor ventilation

The EAACI/GA²LEN Task Force has recently developed recommendations for the management of the allergic child at school (Table 1). A comprehensive approach focused on the child with AR and its comorbidities can provide a comfortable school life (Figure 1).

TABLE 1

Action points (EAACI/GA²LEN Task Force)
Students should be able to take reliever medication for allergic rhinitis (AR) and chronic rhinosinusitis (CRS) at school, as required
Students should not be criticized for frequently displaying symptoms of AR or CRS
Teachers should be aware of increased symptoms of AR or CRS during outdoor exercise activities in peak seasons
Schools should aim to reduce indoor air pollutant sources including allergens, and improve indoor ventilation
Teachers should be aware of and take into consideration the negative effect of AR or of CRS on examination performance.

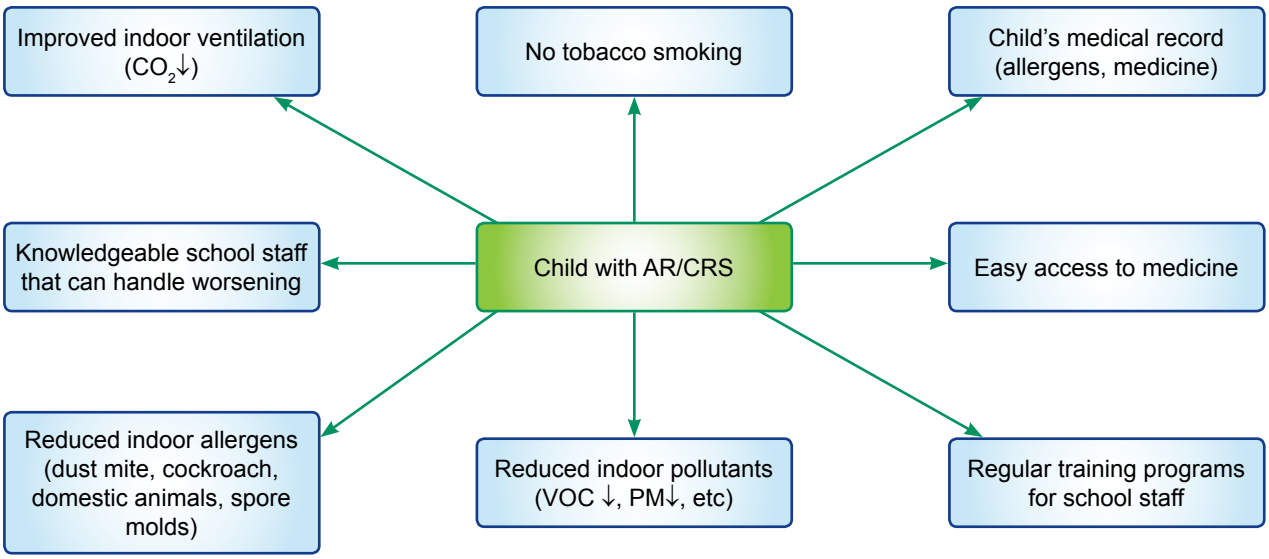

Figure 1 Management of the child with chronic upper airway disease at school.

The head teacher, responsible for school policy, should aim to create an allergy friendly school. Regular education programs about AR and its comorbidities should be arranged to improve knowledge level and attitude of the school staff. Newly admitted students with chronic upper airway disease and comorbid diseases should be identified and recorded during the school registration process. The status of the illness should be checked at the annual re-registrations. Students with chronic upper airway disease are encouraged to have their medications readily available and safely stored at all times. Additionally, relieving medication must be always available in the school. Schools should aim to reduce indoor air pollutant sources including allergens, improve indoor ventilation, and maintain healthy indoor and outdoor air quality.

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12a MANAGING ALLERGIC RHINITIS AND CHRONIC RHINO-SINUSITIS IN DEVELOPING COUNTRIES - FOCUS ON LATIN AMERICA

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KEY MESSAGES

- Allergic rhinitis (AR) is highly prevalent among Latin American countries
- Many factors can contribute to this high prevalence, some of them local and some comparable to other regions worldwide
- Correct management of AR depends on access to trained doctors and treatment available
- There is no data available on sinusitis epidemiology for Latin American countries

Allergic rhinitis (AR) represents probably the most prevalent chronic non-communicable disease globally, as well as in Latin America. The ISAAC study evidenced that over 30% of paediatric population present current symptoms of AR, while almost 20% suffer from current rhino-conjunctivitis, the most indicative epidemiological tool for upper airway atopic condition. The remarkable prevalence of AR in certain Latin American countries positions them among the highest incidence worldwide (Table 1).

There was no significant correlation between markers of country development such as gross national product (GNP), infant mortality rate or environmental pollution, and the prevalence of AR symptoms. However, conditions like environmental tobacco smoke or active smoking could have a detrimental impact in this population (Figure 1).

There is an intriguing report of nasal allergies prevalence below 10% corresponding to 8 Latin American countries, based on telephone interviews asking for AR diagnosis. This wide difference could be attributed to methodology or to under-diagnosis. One of the most common co-morbidity of AR is sinusitis, but no data is available for prevalence of chronic rhino-sinusitis in Latin America.

A survey of 20 physicians and 200 patients from Argentina on the management of AR, showed that more than half of patients had moderate to severe AR, and two out of three had sinusitis, with a similar proportion having a significant impact on the quality of life. Preferred treatment both for patients and physicians (60% of respondents) were oral anti-histamines and nasal steroids, in accordance with first treatment options suggested by guidelines. Nonetheless, 40% of patients received an inappropriate AR management. Scarce availability and poor affordability of essential drugs like nasal corticosteroids in Latin American countries could also explain the elevated prevalence and severity of AR. According to current reports 81 million of children live in poverty in Latin America and appropriate access to a correct evaluation and treatment is not guaranteed at all.

Allergic Rhinitis and its Impact on Asthma (ARIA) initiative is one of the engines promoting the knowledge and management of AR in Latin America, in order to achieve the necessary changes in health policies that finally benefit this huge population affected.

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TABLE 1

Prevalence of rhinitis and related symptoms among Latin-American children according to language they spoke – ISAAC phase three

	N	Rhinitis ever	Rhinitis last 12m	Rhinitis & ocular symptoms 12m	Daily interference 12m	Hay fever ever	Current symptoms RC	Current symptoms of severe RC
6 to 7 yr old								
Portuguese	21,799	32.8	25.6	25.6	2.1	19.3	11.7	1.3
Spanish	72,052	35.1	29.7	13.8	1.7	12.6	13.1	1.1
OR 95%CI		0.96*	0.86*	0.87*	1.33*	1.74*	0.92*	1.27*
		0.93–0.99	0.83–0.89	0.85–0.93	1.19–1.48	1.67–1.81	0.88–0.97	1.10–1.45
Total 13 to 14 yr old	93,851	34.6	28.7	13.5	1.8	14.6	12.7	1.2
Portuguese	58,418	40.2	28.7	15.2	1.2	22.6	13.3	0.8
Spanish	107,499	46.7	37.3	20.9	1.6	13.8	19.5	1.2
OR 95%CI		0.76*	0.68*	0.68*	0.75*	1.81*	0.64*	0.69*
		0.75–0.78	0.66–0.69	0.66–0.69	0.69–0.82	1.77–1.86	0.62–0.65	0.61–0.76
Total	**165,917**	**44.4**	**34.3**	**18.9**	**1.5**	**17.5**	**17.3**	**1.1**

RC, rhinoconjunctivitis.
*Chi-square *p<0.05, **p<0.001*

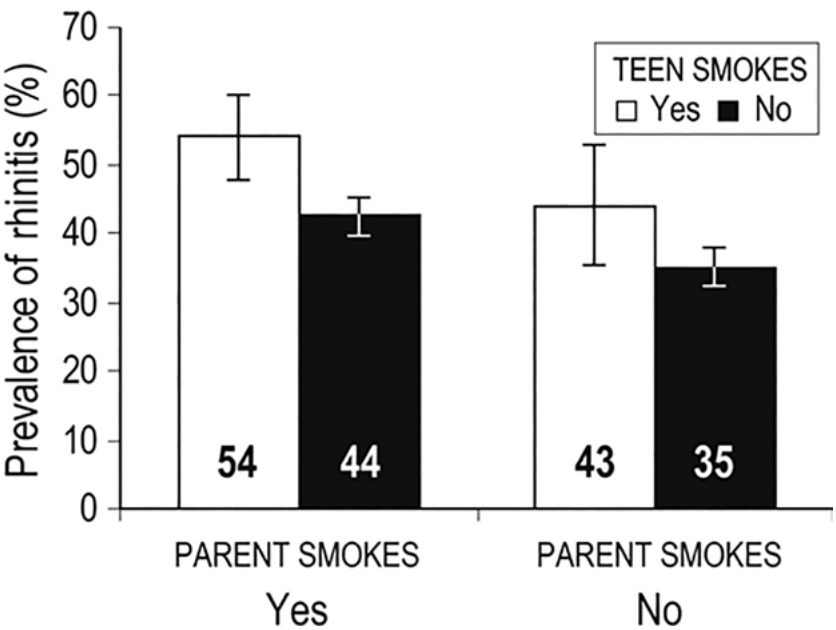

Figure 1 Association of rhinitis with both personal and parental smoking. (From Gómez M, Vollmer WM, Caceres ME, et al. Adolescent smokers are at greater risk for current asthma and rhinitis. Int J Tuberc Lung Dis 2009;13:1023-1028).

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12b MANAGING ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN DEVELOPING COUNTRIES – FOCUS ON EASTERN EUROPE

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KEY MESSAGES

- Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are widespread in Eastern European Countries (EECs) and follow the increasing trend in developed countries
- More epidemiological studies on AR and CRS in EECs are needed
- In EECs networks of specialized allergy centers are set for diagnostics and treatment of AR and CRS

Allergic rhinitis (AR) is the most widespread allergic disease, reaching a prevalence of up to 40% in some developed countries. In the East-European countries (EECs) data on prevalence of AR is rather sparse in comparison to Western Europe, reflecting the lower level of funding for epidemiological projects. In addition, a huge number of subjects, mainly with intermittent and/or mild AR don`t reach the doctor's offices.

Data from classical epidemiological studies on AR prevalence in EECs derive from studies in the 1950-1990s period. In the Russian Federation and the CIS countries prevalence studies were performed using ISAAC approach and revealed a prevalence for AR ranging from 1.4 to 39.7% in different countries (Table 1). Higher prevalence of AR was associated with intense urbanization and industrialization. The survey showed that 1.3-52 % of young children suffer from AR, while the prevalence in older children was 20-26%. For the Russian Federation the prevalence of AR of 13-39% was found in children and adults depending on climate, geographic and ecologic features of the region. In the last 20 years, the prevalence of AR in the Russian Federation increased 4-6 times, peaking at the age of 18-24. The incidence of AR in Ukraine was 22% and of CRS of 20-40%. The urban population was more frequently affected with 20% of nearly 8 million people compared to the rural population where 14% presented with AR. In Belarus, the AR prevalence was nearly 4%, with children more frequently affected (5.6%). In Poland, almost 25% of adult population was affected by AR and 16% by CRS. A study on 933 patients in Hungary found that 52.5% of patients suffered from seasonal AR and 35.1% from perennial AR. In Bulgaria the prevalence of AR was found to be 16%, more than half associated with pollen sensitization.

The main risk factors for the development of AR in EECs depicted by the surveys were family history of atopy, sensitization to allergens, smoking, air pollution and climate factors. In Russia, Belarus, Poland, Bulgaria and most other EECs networks of specialized allergy centers for diagnostics and treatment of AR are set in place or under development. A deficiency in the EECs is the insufficient use of educational programs for AR and CRS. The main disease-modifying treatment of AR is allergen immunotherapy.

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TABLE 1

AR and CRS prevalence in EECs

Country	AR	CRS	Survey
Russia	13-39%	15%	Khaitov RM, 1998 Ivanchenko OA, 2012
Ukraine	22%	20 – 40%	Pukhlik BM, 2008
Belarus	3.84%	9.71	Shpakou A, 2012 Xoxa PH, 2014
Moldova	4.8 – 9.8%	-	Andriesh LP, 1994
Bulgaria	16%	-	Mileva J, 2000
Hungary	35.1-52.5%	-	Szilasi M, 2012
Poland	25%	16%	Wardas P, 2014
Romania	14%	13 %	Grigoriu IC, 2013

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12c MANAGING ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN DEVELOPING COUNTRIES - FOCUS ON ASIA PACIFIC

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KEY MESSAGES

- Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) have a significant impact on quality of life of the affected patients in the Asia Pacific region and their prevalence is expected to continue its increase
- For both AR and CRS there are significant treatment gaps, challenges and unmet needs in Asia Pacific region
- Patients needs and expectation differ from present treatment options
- There is an urgent need to improve patient knowledge of treatment and management options
- Guidelines on treatment may need to be tailored according to regional situation in allergy

INCIDENCE & MANAGEMENT

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) still remain largely undertreated in Asia Pacific, which currently reigns amongst the most populated regions of the world. The dense population is further compounded by rapid economic development, urbanization and the subsequent environmental pollution. The true incidence and prevalence of AR and CRS in the Asia Pacific is difficult to determine given the vast region with different socio economic and health care systems.

The Allergies in Asia-Pacific Survey, which was published in 2011 reported an overall prevalence of 8.7% for the physician-diagnosed nasal allergy in eight countries in the region after screening of 33378 households, with 1043 adults and 192 children included in the survey. The prevalence varied from that reported for the developed countries to the developing countries, underlying the diversity in Asia Pacific. The prevalence ranged from 13.2 % in Australia, to 9.1% in China, 9.6% in Taiwan, 7.1% in Malaysia to 12.3 % in Vietnam and 2.5% in Philippines. AR affected both adults and children, and the average age at diagnosis was 26 years for adults and 9 years for children.

The geography of Asia Pacific, with the majority of the countries having a tropical and subtropical climate, influence the type of predominant AR, with 66% of patients having intermittent or seasonal AR (SAR), and only 30% reporting persistent or perennial AR (PAR) (Figure 1).

The majority of the patients were treated by general practitioners (40%) and by ENT physicians (40%), with only 2-3% managed by allergists or respiratory physicians. Investigation of allergy was not routinely performed, with 42% having had no allergy investigation at all. When allergy testing was done 9% were skin prick tested only, 14% blood tested only and 17% had both tests performed.

BURDEN OF DISEASE AND IMPACT ON QUALITY OF LIFE

The burden of AR and CRS is well documented and is increasing in Asia Pacific with significant impact on quality of life (QoL), notably by interference with work and school performance, productivity, daily life, and sleep (Figure 2). Reports show that AR significantly troubles 96% of adults and of children. The most bothersome symptoms included nasal congestion (78%),

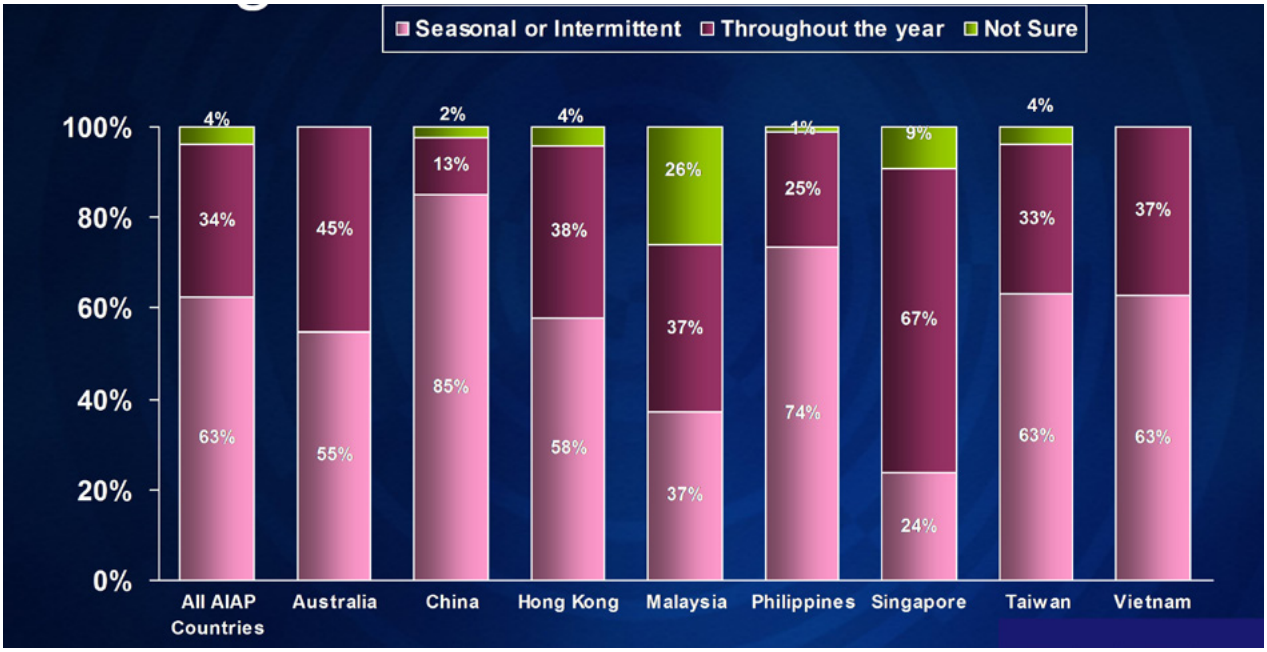

Figure 1 Intermittent or perennial allergies in Asia Pacific.

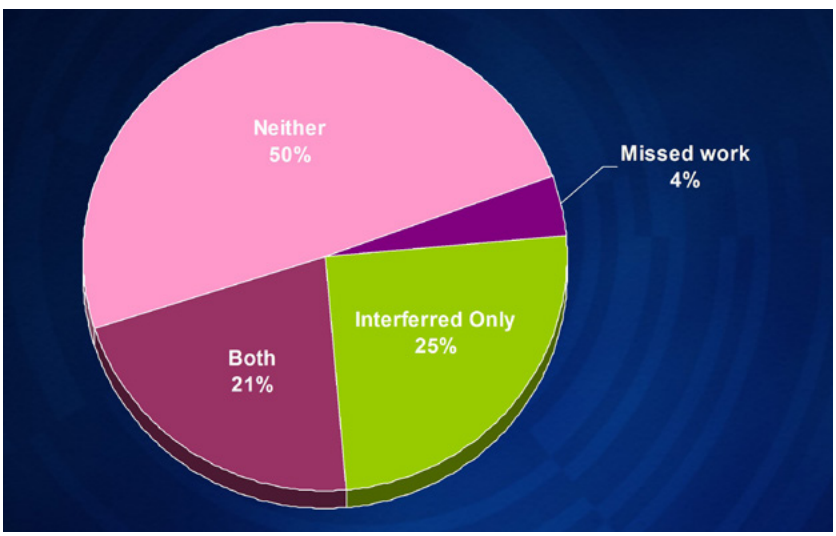

Figure 2 Interference with work due to allergic diseases.

rhinorrhea (74%) and sneezing (71%). Only 41% of adults and 47% of children felt their symptoms were controlled, thus it is of no surprise that work productivity decreased from 88% to 63% when the patient had AR (Figure 3).

The impact of AR on the quality of sleep is well recognized with over 70% of the adults and 60% children indicating sleep related disturbances (Figure 4).

Up to 41% of children find their nasal allergy interfering or preventing them from attending school, with reduction of school performance from 86% to 66%. Nearly 85% of children reported a significant impact of allergies on their day-to-day life.

Given the huge population potentially affected by AR and CRS in Asia Pacific it might be speculated that the lost productivity and the economic consequences may be significantly higher compared to other regions.

TREATMENT PARADIGM, UNMET NEEDS AND PATIENTS PERSPECTIVE

The treatment of AR and CRS is well established by guidelines. Despite this, reports reveal that patients in this region are not achieving adequate control of their symptoms with up to 58% of adult patients claiming that their allergies are not optimally controlled despite medication. Although up to 67% of patients were on some form of treatment for their symptoms. The usage of intranasal corticosteroids (INS) was surprisingly very low (19-20%), despite guidelines clearly

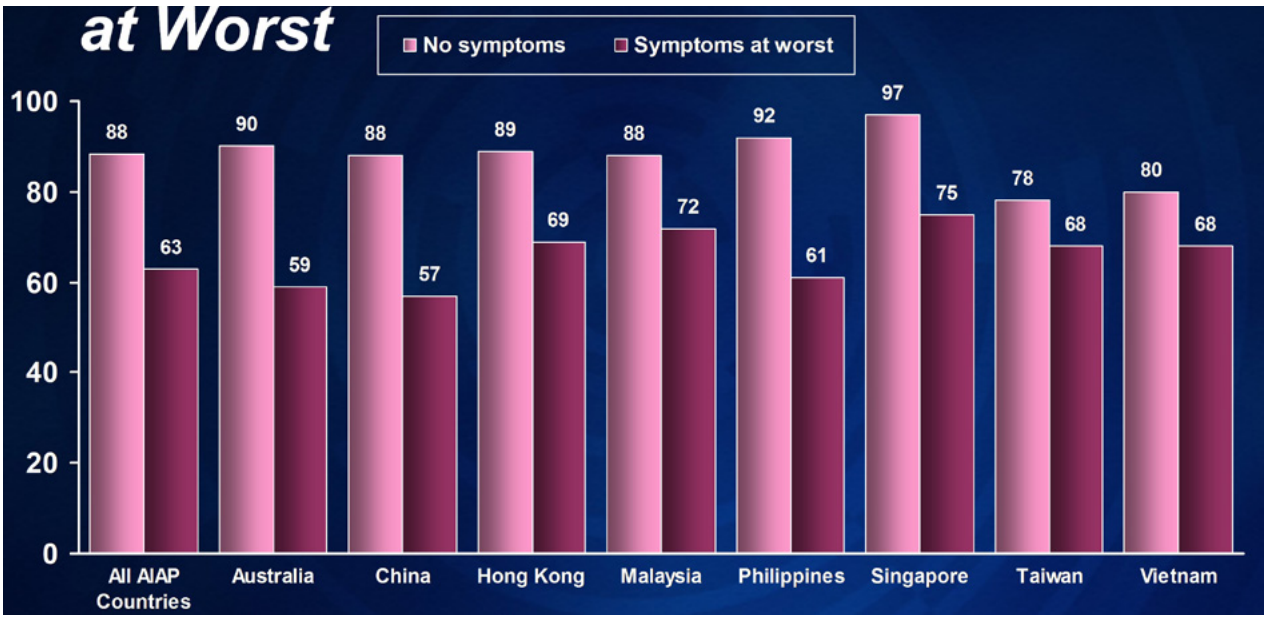

Figure 3 Reduction of work productivity due to allergic rhinitis.

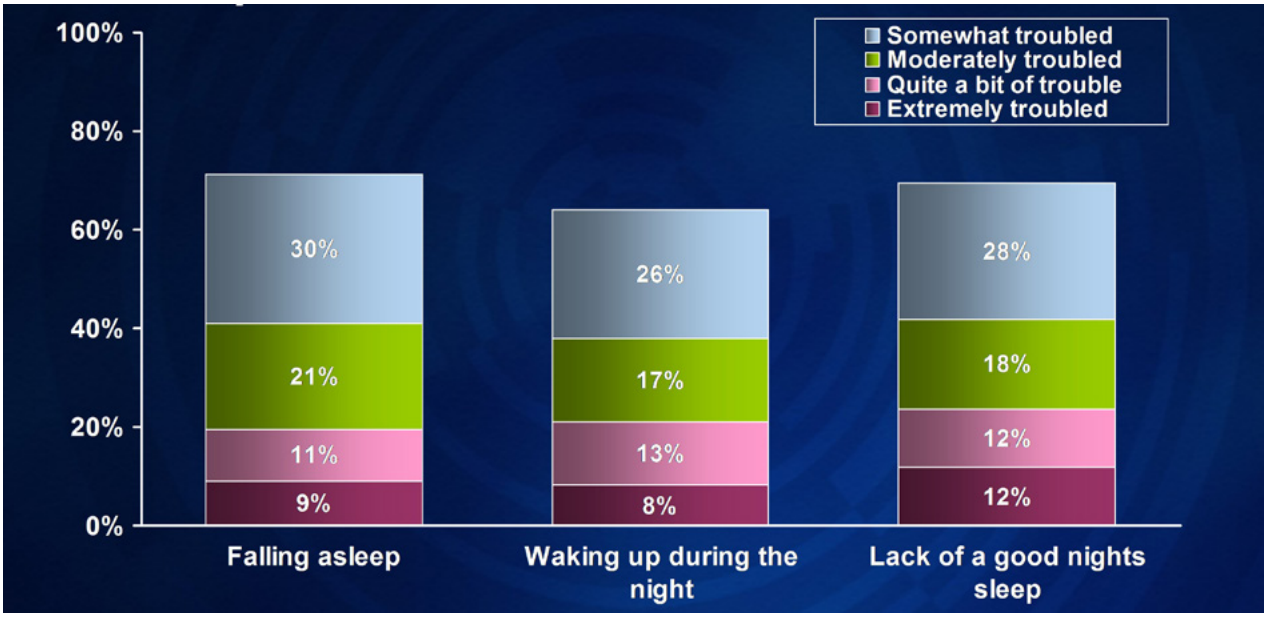

Figure 4 Interference with sleep in AR.

suggesting their usage as the gold standard for moderate to severe AR. Thus, the unsatisfactory level of disease control, may be due to the lower usage of INS as the primary treatment of choice. Even among the patients on INS, only 27% were very satisfied with their steroid nasal spray. Reasons for dissatisfaction included low efficacy (72%) and lack of 24-hour relief (15%) (Figure 5). Some patients were compliant to the prescribed INS due to their concerns about side effects, long-term use, or due to loss of efficacy over time.

Contrary to popular perception that cost would be an issue in Asia Pacific, cost was not reported as a major factor among uncontrolled patients. Low patient education and awareness appears to be equally important, as only 20% of patients claim to have some infor-

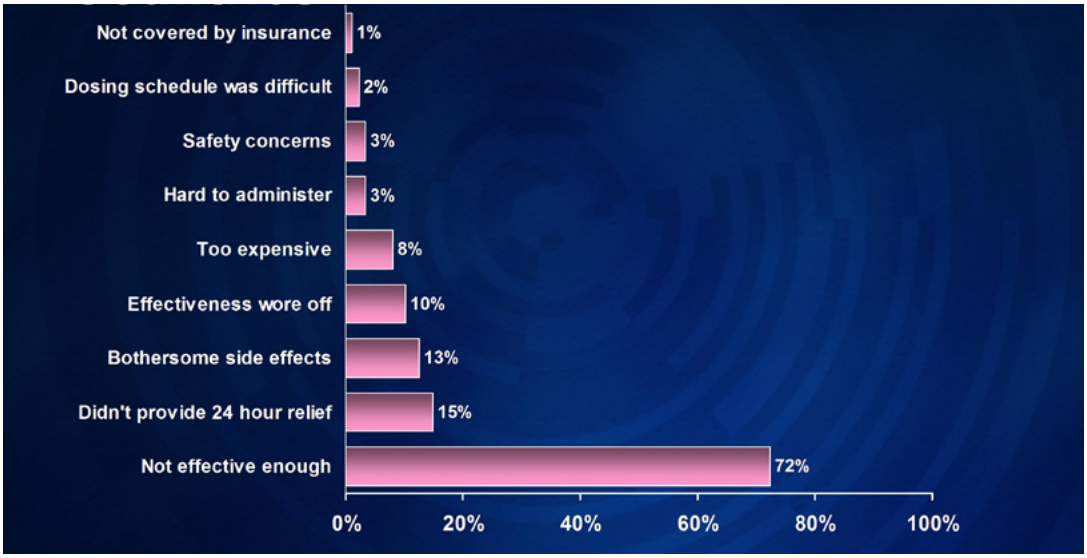

Figure 5 The reason patients were dissatisfied with their nasal spray.

mation about INS and up to 50% of patients reported that they have never been shown how to use their nasal spray. It is also interesting to note that up to 40% of patients visit and get advice on allergy from their pharmacist, thus education on AR management should be provided to all health care professionals (HCP) and not restricted to medical doctors alone.

FUTURE DIRECTION AND CHALLENGES

The prevalence of AR and CRS in Asia Pacific will continue to rise drastically in tandem with the exponential economic growth and urbanization in this region. Increased risk factors for atopy associated with congested modern urban living, predominant in major Asian cities, in parallel with increased environmental pollution will increase the total burden of allergic diseases on the already precarious health care systems in this region. Asia Pacific is unique in the fact that it contains a highly diverse population, with marked variation in the genetic background as well in the living environments.

There may be a need to tailor the existing guidelines according to the different needs and challenges in this region. A recent study on the acceptance of the ARIA guidelines, that is widely used by the HCP in Malaysia, revealed that although the majority complied with the guideline, up to 34% of ENTs, 42% of pharmacists and 11% of general practitioners felt that there was a need to tailor the guidelines to suit the regional problems and allergens.

CONCLUSION

Both AR and CRS have significant impact on the heath care systems in Asia Pacific, with a similar disease burden as for the rest of the world and with up to 90% of patients reporting an impact on quality of life. The rapid economic growth with corresponding pollution and urbanization will increase the prevalence of allergic disorders, with increasing socio-economic impact in the future.

There is an urgent need to acknowledge the significant the impact of these disorders on societal costs and the differences in the treatment paradigm, challenges and unmet needs for the different areas in the region. Poor patient and HCP education has a significant negative impact. Guidelines on treatment of allergic diseases need to be adapted according to the local needs and challenges.

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12d MANAGEMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN DEVELOPING COUNTRIES - FOCUS ON AFRICA

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BURDEN OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN AFRICA

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) are prevalent non communicable diseases increasing around the world, even in Africa. These chronic diseases confer a significant burden through direct or indirect symptoms, complications and cost.

In contrast to developed countries, the government health program of many African countries focus only on transmissible diseases, malnutrition, maternal and infant mortality, while data on respiratory diseases remain scarce. The prevalence of AR is very high (>35%) among Nigerian Africans, and it is likely that environmental factors are responsible for major differences with other countries. AR prevalence is much higher in urban area, especially in capital cities from Africa. CRS is not less common. The advent of HIV-AIDS has further worsened the incidence of CRS in Africa.

Local allergens related to African environmental settings are not well known. House dust mites and cockroaches are reported as major allergens in Africa, while pollen allergens remain poorly described.

KEY MESSAGES

- The prevalence of allergic rhinitis (AR) and of chronic rhinosinusitis (CRS) in African countries is increasing due to increased urbanization and pollution. The advent of HIV-AIDS has further worsened the incidence of CRS in Africa
- The diagnosis of AR in Africa is largely clinical, due to the non-availability of allergy tests in most countries. Screening for AR using total serum IgE can be deceptive in Africans since helminthic infections, rather than genetic factors, may be responsible for the increase in the total serum IgE levels
- Because of contending socioeconomic challenges, most patients are unaware of their AR and CRS. Coupled with out-of-pocket payment for healthcare cost, presentation to the hospital is often delayed, and it is not uncommon for complications to be present at diagnosis
- Treatment is based on the availability of essential drugs and their financial affordability, thus allergen immunotherapy for AR or endoscopic sinus surgery for CRS are not easily available

AR predisposes to development of other airway comorbidities such as allergic asthma, rhinosinusitis, nasal polyposis, adenoid hypertrophy and otitis media. Table 1 shows an overview of AR and related diseases in Africa.

Both AR and CRS significantly affect the quality of life of Africans through direct cost (payments to doctors for frequent consultations, prescribed medications, over the counter (OTC) drugs, alternative and complementary drugs), indirect costs (loss of work hours and school days) and intangible costs (loss of quality of life, pain and suffering, psychological maladjustment, social costs). These costs become significant in countries with high prevalence of allergy and low per capital income, as seen both in the Anglophone and Francophone African countries.

TABLE 1

Overview of prevalence of allergic rhinitis and allergic related diseases in African Countries

Country, city	Author, year	Study population	Age	AR*	AR**	Rhinitis**	RC**	Wheeze**	Eczema**
Morocco	El KS et al. 2009	Rural Population			37.8				
Morocco Casablanca	Ait-Khaled N et al. 2007	Schoolchildren	13-14				28.1	16.0	23.0
Tunisia, Tunis	Khaldi F et al. 2005	Schoolchildren	13-14				27.7		
Tunisia, Grand Tunis	Ait-Khaled N et al. 2007	Schoolchildren	13-14				14.7	15.4	13.0
Egypt, Cairo	Georgy V et al. 2006	Schoolchildren	nov-15				15.3		
Urban Ivory Coast	Ait-Khaled N et al. 2007	Schoolchildren	13-14				27.6	19.3	18.2
Togo, Loné	Ait-Khaled N et al. 2007	Schoolchildren	13-14				14.6		
Nigeria	Desalu OO et al. 2009	General population	18-45		29.6				
Ethiopia, Gondar	Hailu S et al. 2003	Schoolchildren					14.5		
Kenya, Nairobi	Ait-Khaled N et al. 2007	Schoolchildren	13-14				19.8		
Kenya	de SM et al. 1994	Patients		48.6					
Kenya	Esamai F et al. 2002	Schoolchildren	13-14		38.6				
Kenya, Nairobi	Ait-Khaled N et al. 2007	Schoolchildren	13-14				19.8	18.0	14.9
Gabon	Ait-Khaled N et al. 2007	Schoolchildren	13-14				16.5		
Uganda, Ibanda	Ait-Khaled N et al. 2007	Schoolchildren	13-14				16.4	13.0	7.7
Cameroon, Yaounde	Ait-Khaled N et al. 2007	Schoolchildren	13-14				8.9	5.7	7.7
Congo, Brazzaville	Ait-Khaled N et al. 2007	Schoolchildren	13-14				33.3	19.9	16.2
Democratic Republic of Congo, Kinshasa	Ait-Khaled N et al. 2007	Schoolchildren	13-14				11.8	7.5	10.9
Democratic Republic of Congo, Kinshasa	Nyembue TD et al. 2012.	General population	5-83	13.9		30.8	24.4	15.4	6.2
Democratic Republic of Congo, Kinshasa	Nyembue TD et al. 2012.	Patients	4-89	23.9					
Zimbabwe	Kambarami RA et al. 1999	Children	< 2	15.6					
Zimbabwe	Sibanda EN et al. 2003	Patients	1-62	33.0					
South Africa, Cape Town	Ait-Khaled N et al. 2007	Schoolchildren	13-14				20.7	20.3	13.3
South Africa, Cape Town	Mercer MJ et al. 2004		13-14		33.2				

*Data expressed in percentage, AR: allergic rhinitis. RC: rhinoconjunctivitis. *: diagnosis clinically confirmed via either skin prick testing or by specific-IgE in serum. **: 12-month prevalence.*

TABLE 2

Risk factors for allergic rhinitis identified by two African studies	
Desalu et al, (2009)	**Olusesi, Amodu & Said, (2007) ***
Dust (55.8%)	Dust (65%)
Kitchen Fumes (20.7%)	Smoke (60%)
Cold Weather (10.6%)	Perfumes (49%)
Smoke (5.1%)	Cold Weather (27%)
Fuel (gasoline) (4.6%)	Red Wine (22%)

**Multiple allergy trigger reported by many patients*

RISK FACTORS FOR AR AND CRS AMONG AFRICANS

Several risk factors are known to relate to AR. These include the genetic background, cigarette smoke, chemicals, cold temperatures, humidity, wind, pollution, hairspray, wood smoke and fumes. A comparison of risk factors for AR from two studies from Africa is shown in Table 2. Added to these known risk factors are poverty, poor education on how to avoid risk factors and poor health infrastructures, which are known to be prevalent in Africa, and which further increase the burden of the disease.

PECULIARITIES OF AR AND CRS AMONG AFRICANS

Urban migration of rural workers is increasing pollution in urban areas, and further amplifies the incidence of AR and CRS. The lack of information on allergic diseases in Africa can be explained by the shortness in physicians and other personnel trained in allergy diagnosis and management. Due to financial constraints, AR and CRS patients are primarily seen by nurses or by the general practitioners; the education of GPs in some African countries is highly limited regarding ear, nose and throat diseases in general, and AR and CRS in particular.

The diagnosis of AR in Africa is largely clinical, due to the non-availability of allergy tests in most countries. Allergen-specific serum IgE is measured in a very limited number of private laboratories, and thus is unaffordable to most patients. Screening for AR using total serum IgE can be deceptive in Africans since helminthic infections, rather than genetic factors, may be responsible for the increase in the total serum IgE levels.

Because of contending socioeconomic challenges, most patients are often unaware of their AR and CRS. Coupled with out-of-pocket payment for healthcare cost, presentation to the hospital is often delayed, and it is not uncommon for complications to be present at diagnosis (Figure 1). Overall the management of AR and CRS in many African countries is poorly developed and the quality of care offered is often at a low standard. Only some countries have implemented evidence-based guideline recommendations. Treatment of AR follows the ARIA guidelines in most tertiary care centers.

In most African countries, pharmaceutical practices are unregulated, resulting in unfettered access to OTC drugs and other regulated drugs, with management of AR and CRS not based on sound evidence. Treatment is based on the availability of essential drugs and their financial affordability. For example, chlorpheniramine and beclomethasone are part of the WHO essential drugs list and diseases are available and subsidized, while, antileukotrienes and anti-IgE are not used in many low income countries. Antibiotic treatment such as amoxicillin-clavulanate is frequently used for CRS compared to others antibiotic classes due to its availability in deprived countries. Finally endoscopic sinus surgery is expensive and needs a specific training. Allergen-specific immunotherapy is not easily accessible because of lack of trained specialists and unknown regional allergens.

Depending on cultural and social barriers patients seek self-treatment and unproven traditional therapies. There is widespread use of alternative and complementary therapy, largely because they are cheaper, and also because of local beliefs.

Figure 1 Right upper-lateral orbital abscess complicating chronic rhinosinusitis (pre- and postoperatory).

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12e

MANAGING ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN DEVELOPING AND LOW INCOME COUNTRIES - FOCUS ON SOUTH ASIA

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"Allergy" and "rhinitis" are very commonly used medical terms in South Asia. These terms are even used when there is no evidence of allergy, as the cause of any rhinitis symptoms, hence they are over-reported. On the same note, the term "rhinosinusitis" is newer and thus less diagnosed.

Specific allergy diagnostic facilities are scanty in the South Asia region, hence the diagnosis of allergic rhinitis (AR) is more often a clinically empirical diagnosis. In India, AR is rarely given the importance it deserves and is considered to be a trivial disease, despite the fact that symptoms of rhinitis have been noted to be present in 75% of children and 80% of asthmatic adults and despite it's profound impact on the quality of life.

According to the skin allergy testing data, house dust mites (*Dermatophagoides farinae*) are the commonest cause of AR. In addition many allergens are more frequently encounterd in South Asia, such as the allergenic pollens from the common paper mulberry tree, cannabis and Parthenium in some areas of Pakistan and India, where they reach significantly high quantities in the air (Figures 1 a, b & c). Similarly, the production of highly

KEY MESSAGES

- Allergic rhinitis (AR) is overdiagnosed, chronic rhinosinusitis (CRS) is less diagnosed
- Specific allergy testing facilities are scanty
- House dust mites are the most common allergen causing AR, however specific allergens are noted such as paper mulberry tree, cannabis and Parthenium or highly allergenic dusts from mechanically operated wheat threshers
- The choice of treatment of AR and CRS is limited by several factors, and their management is often not appropriate

Figure 1 A - *Paper mulberry*; B - *Parthenium*; C - *Cannabis*.

Figure 2 Wheat threshing.

allergenic dusts from mechanically operated wheat threshers (Figure 2) or rice huskers in South Asia can affect patients several miles downwind in wheat & rice growing countries.

Studies in India have shown that 63–89% of adults with AR and 65% of children have underlying chronic rhinosinusitis (CRS) and nasal polyps (NP). Even when the presence of NP and CRS in AR is sought for, inadequate treatments, both medical and surgical, along with troublesome adverse effects of the medications add to the problem.

Although topical corticosteroids are now increasingly being recognized as the cornerstone of the treatment for AR, in most of the South Asian countries, anti-histamines still form the first line of treatment. Both first and second generation anti-histamines are commonly used.

The choice of treatment is limited by several factors. Cost is a major factor, and includes the cost of the drug itself and the doctor's fee plus the logistical costs of accessing healthcare (for example travel expense), as well as the possible adverse effects. Hence, many patients prefer to visit alternate medicine practitioners, for relief of their ailments.

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12f MANAGING ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS IN DEVELOPING COUNTRIES – FOCUS ON EAST ASIA

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KEY MESSAGES

- With the rapid economic development of the East-Asia countries, the prevalence of allergic rhinitis (AR) and chronic rhinosinusitis (CRS) have increased rapidly and demonstrated wide inter- and intra-regional differences
- The predominant CRS endotype in Asian subjects is characterized by a Th17 cell-mediated predominance of neutrophils
- Besides the use of therapies recommended by guidelines, the treatment of AR and CRS in East Asia also includes acupuncture and traditional Chinese medicine
- Optimal treatment for AR and CRS in East Asian's should be tailored based on evaluation of the patients' clinical phenotypes and endotypes

Despite the presence of a markedly denser population compared to western countries, there is little epidemiological data on allergic rhinitis (AR) and chronic rhinosinusitis (CRS) prevalence in the East-Asia region, especially in China. The majority of the studies on AR in this region have primarily investigated the prevalence of disease in children and demonstrated wide inter- and intra-regional differences (Figure 1). Along with the rapid economic development of the East-Asia countries the lifestyles of the citizens have become more westernized in terms of urbanization and dietary habits, and the prevalence of upper airway diseases such as AR and CRS have increased rapidly. The potentiating effect of the considerable increases in air pollutant levels on the rising prevalence of the respiratory disorders cannot be ignored (Figure 2).

As wide varieties of grass/tree pollen and/or mites are present in the different regions, these play an important role as traditional sensitizing allergens in the development of AR in East Asia. A number of studies from Japan suggest Japanese cedar pollen to be the most prevalent and important sensitizing agent across Japan, with seasonal AR caused by Japanese cedar pollen (i.e. sugi-pollinosis) being considered a national affliction. In China, dust mites and *Artemisia* pollen (Figure 3) have been reported as the most common perennial and seasonal cause of AR.

While the mucosal inflammatory processes in Caucasian subjects with CRS are mainly orchestrated by Th2 cytokines and are characterized by an increased tissue eosinophilia and local IgE production, the predominant endotype in Asian subjects with CRS with nasal polyps (CRSwNP) is characterized as a Th17 cell-mediated predominance of neutrophils. However, it has been demonstrated that there is a shift over time from the predominantly neutrophilic to an eosinophilic response in Asian CRSwNPs patients.

Besides the use of therapies recommended by the evidence-based Allergic Rhinitis and its Impact on Asthma (ARIA) and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012 guidelines, the treatment of AR and CRS in East Asia also includes acupuncture and use of traditional Chinese medicine involving some herbal medicines or formulae,

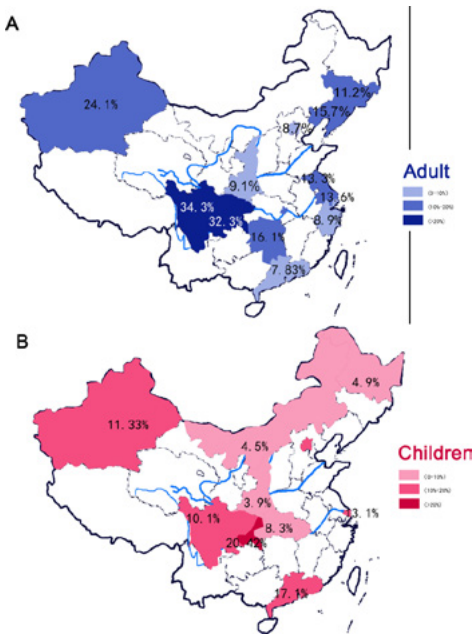

Figure 1 Prevalence of allergic rhinitis in adults and children in different cities in China.

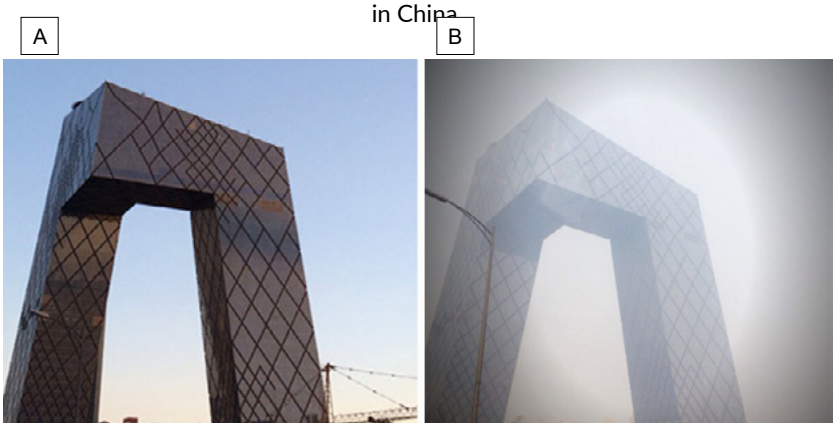

Figure 2 China central television (CCTV) headquarters in non-haze day (A) and in haze day (B).

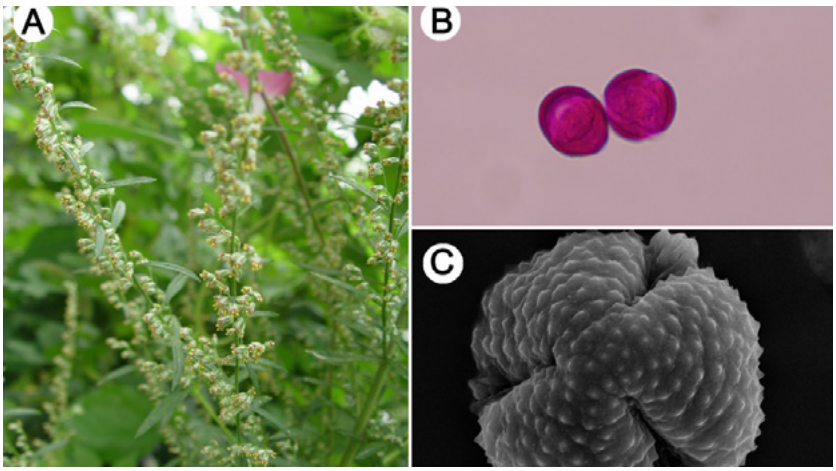

Figure 3 *Artemisia* pollen. A: The blooming *Artemisia*. B: *Artemisia* pollen (magnification ×400). C: *Artemisia* pollen by scanning electron microscope.

which have been reported to be effective for AR.

However, more emphasis on the importance of allergen immunotherapy for AR and pharmacotherapy for CRS is required for treatment of AR and CRS in East Asian countries. Furthermore, optimal treatment for AR and CRS in East Asian should be tailored according to the patients' needs, based on careful evaluation of their clinical phenotypes and endotypes, which may contribute to the choice of therapeutic strategy and thus influence the treatment efficiency.

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13 BEST BUYS FOR ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS PREVENTION AND CONTROL

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KEY MESSAGES

- Allergen avoidance measures and allergen immunotherapy are probably the best two "buys" for prevention and control of allergic rhinitis/rhinosinusitis as they target the underlying cause of the allergic inflammation
- Studies in which allergic patients were moved to an allergen-free environment were successful
- Allergen avoidance and associated costs should be balanced with the individual burden of the disease
- Both allergen avoidance and immunotherapy require the identification of the allergen causing the symptoms; therefore seeing an Allergy specialist is crucial to obtaining an appropriate and cost-effective treatment

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) cause major illness and disability worldwide. These conditions impair patients' quality of life (QoL), cause sleep disturbance and, through loss of work and school attendance, are responsible for an enormous lost in productivity annually. Thus, the indirect costs of both these diseases are substantial. Direct costs are also high, mostly from medication use, but are often underestimated because many products to allegedly treat these diseases are sold over-the-counter. The general belief that nasal symptoms are "normal" leads patients to avoid seeing a doctor and to buy over-the-counter products; however, there may be more cost-effective ways of treating these conditions in the long-term.

There are two main strategies for etiological treatment of AR and CRS: allergen avoidance and allergen immunotherapy (AIT). Both approaches are disease-modifying and require the identification of the allergen causing the symptoms, either by skin prick test or serum specific IgE detection.

Some studies have suggested that allergen avoidance is not effective for the treatment of allergic respiratory disease, but this was probably due to the fact that allergen avoidance was not complete. Studies in which allergic patients were moved to an allergen-free environment, such as a high-altitude village or a hospital room, were indeed successful. Allergen avoidance involves different measures depending on the allergen in question, but general measures can be beneficial to control exposure to a range of indoor allergens (Figure 1). Examples include minimizing allergen reservoirs, such as carpets and sofas, keeping the home dry, maintaining good ventilation, regular cleaning of surfaces, room air filters and masks. Use of acaricides and extensive bedroom-based environmental control measures may provide some benefit in reducing symptoms in house dust mite perennial AR. Nasal irrigation may be useful as an adjunctive treatment of AR during unavoidable exposure to airborne allergens and pollutants.

To achieve successful allergen avoidance patients' education to follow the recommended measures is essential, which can be complemented with written instructions, visual aids and home visits, where practical advice can be provided and demonstrated. However, allergen avoidance and its costs should be balanced with

Figure 1 Allergen avoidance in allergic rhinitis. A. Indoor allergens (upper row): pets, moulds and house dust mites). Patients sensitized to indoor allergens who have identified allergens that correlate with their rhino-conjunctivitis symptoms may benefit from environmental control measures (eg, removal of pets, the use of air filtration systems, bed covers and acaricides). B. Outdoor allergens (lower row): tree and/or grass pollens: during plant pollination seasons exposure to the small airborne pollen particles is practically unavoidable on outdoor activities; nevertheless, identifying the clinically relevant sensitizing pollens and following their pollination calendars (https://www.polleninfo.org/en/laenderauswahl.html) may help rhinitis patients to better plan outdoor activities and their preventive and symptomatic medication during peak pollen exposure days.

the burden of the disease.

Allergen immunotherapy can modify the immune response to allergens (Figure 2) and is especially indicated in moderate/severe rhinitis uncontrolled by allergen avoidance and adequate evidence-based pharmacologic treatment.

In summary, allergen avoidance measures and allergen immunotherapy are probably the best two "buys" for prevention and control of allergic rhinitis/rhinosinusitis as they target the underlying cause of the allergic inflammation.

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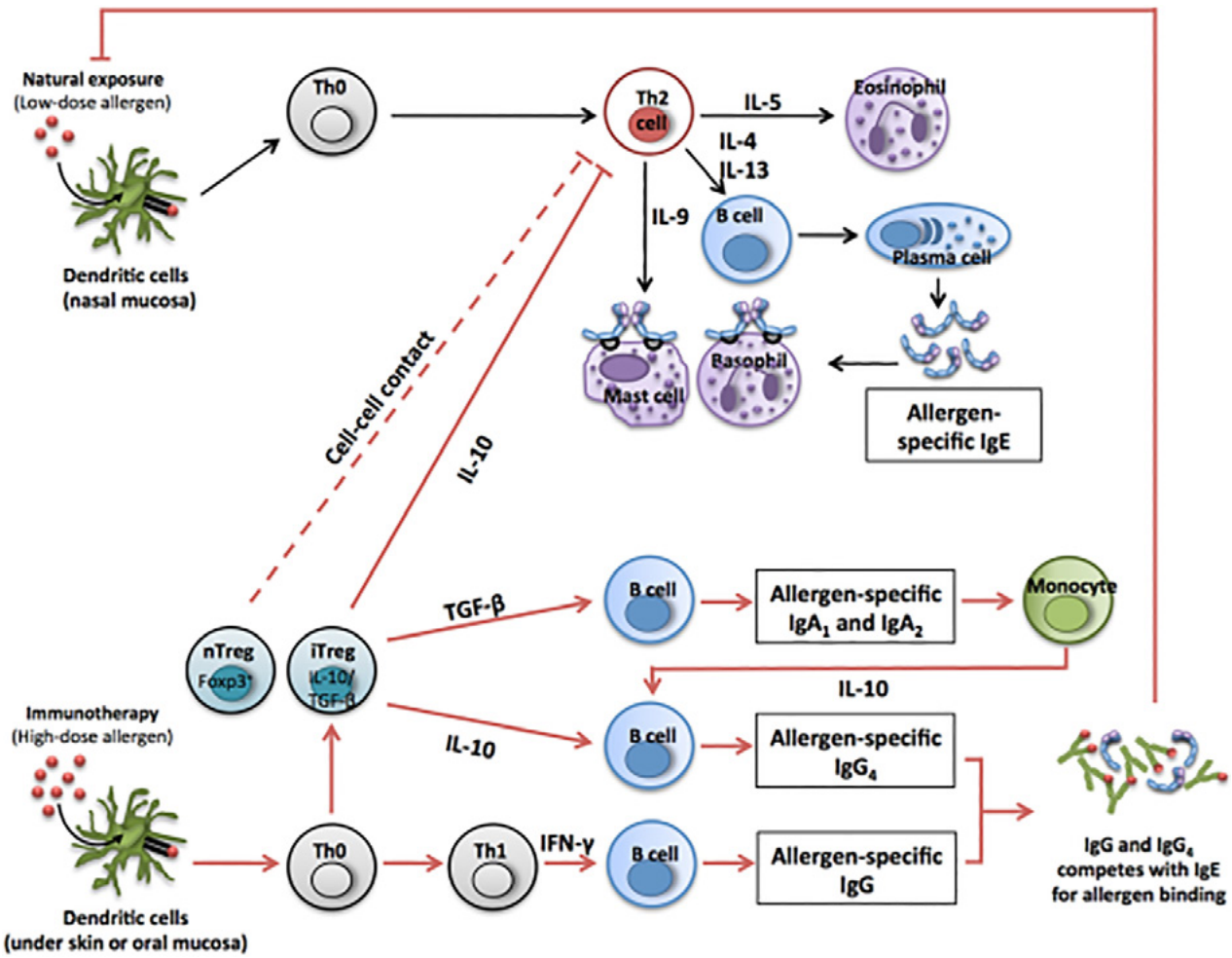

Figure 2 Immunological mechanisms of allergen immunotherapy to aeroallergens. Low-dose and repeated allergen exposure at mucosal surfaces in atopic individuals drives type I IgE-mediated allergic responses. High-allergen dose through a subcutaneous or a sublingual route results in the shift of T cell polarization from a T helper 2 (Th2) to a T helper 1 (Th1) response. This is accompanied by an increase in the ratio of Th1 cytokines (IFN-γ, IL-12) to Th2 cytokines (IL-4, IL-5 and IL-13). The induction of T regulatory cells [inducible Treg cells (iTreg) and natural Treg cells (nTreg)] and cytokines such as IL-10 and TGF-β following immunotherapy play an important role in suppressing Th1 and Th2 responses and contributes towards the induction of allergen-specific IgA1, IgA2 and in particular IgG4 antibodies with inhibitory activity. IgG4 antibodies are able to suppress FcεRI- and CD23-mediated IgE-facilitated allergen presentation and basophil histamine release. (*Reproduced with permission from Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. Clin Exp Allergy 2011;41:1235-1246 with permission from Willey Blackwell.*)

14 THE ROLE OF THE ALLERGIST IN ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Correct and complete diagnosis of allergic diseases requires standardised equipment, well trained personnel and experienced allergists
- The allergist has an unique arsenal of therapeutic measures, be it preventive advice, drug treatment, allergen immunotherapy (AIT) or application of biologicals
- For patients with severe or complex forms of rhinitis or rhinosinusitis the Allergy Centre offers the best diagnostic and therapeutic possibilities
- Continuing medical education of all health care professionals

When allergic rhinitis (AR) symptoms occur in relation to specific exposures, are reproducible, and are absent without exposure, the diagnosis is easily made. When, however the relation between exposure and symptoms is not so clear, allergy may, or may not be relevant since exposure to irritants, infection, anatomic factors, drug and medication abuse etc. may mimic allergy. Thus, to diagnose and treat upper respiratory and ocular allergy, not only allergy tests but also knowledge and experience of a specialist are required.

The diagnosis of allergic diseases is based on a very careful medical history, physical examination and skin and laboratory tests, using standardized commercial or sometimes native allergen preparations, both for skin testing and provocation. Proof of sensitisation (positive skin test or specific IgE) is in principle a prerequisite for the diagnosis of AR, but these tests may also fail to identify allergy or to implicate the allergen as the main cause of patients' symptoms. When proof of sensitisation is absent while the medical history is characteristic of allergy or is discordant with the clinical history provocation tests may be helpful.

The allergist has access to a specialist laboratory, where sensitisation, cross reactivity between allergens and allergen exposure can be investigated. The recent introduction of component resolved diagnosis offers new opportunities for improved accuracy in laboratory testing. The modern allergist is qualified to recommend, perform and interpret the results of such diagnostic tests.

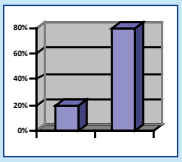
The allergist has an unique arsenal of therapeutic measures, be it preventive advice, drug treatment, allergen immunotherapy (AIT) or application of biologicals. Patients should be informed accurately about how medication should be used (as needed or prophylactic) and the benefits and side effects that can be expected from each type of medication. AIT has been shown to be remarkably effective in patients with rhino-conjunctivitis to pollens, mites, dander and/or moulds. AIT, although very safe when administered properly can also provoke severe allergic reactions. For all of these reasons, it requires a specialised setting and good knowledge about indication and contraindications. With respect to injection AIT, the treatment should be performed by qualified medical personnel under direct supervision of the specialist. Sublingual AIT starts in the allergy practice and continues at home.

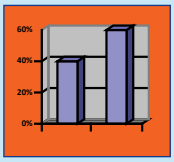
There are significant differences in the way AR is managed in primary

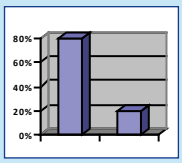
TABLE 1

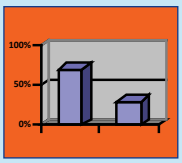
Short survey showing the differences in managing allergic rhinitis between the primacry care physician and the allergy specialist

	Question 1: Do you perform anterior rhinoscopy in patients with allergic rhinitis?		Question 2: Do you perform Peak Expiratory Flow (PEF) or Flow Expiratory Volume 1sec. (FEV1) in your patients with allergy rhinitis?	
	YES	NO	YES	NO
GPs	20%	80%	40%	60%
Allergists	80%	20%	70%	30%









care compared to an allergist setting (Figure 1). On the other hand AR is so prevalent that allergists neither could nor should see all patients. Only specific patients should be referred to the allergist. These patients may require lung function and or allergen provocation testing and further tests aimed at food, drug or occupational allergy. Very often these patients can be referred back with therapeutic advice after consultation.

Allergists have the responsibility to ensure the best management for the allergic patients catered for in their region. This implies that allergists should help to create a local network, where general practitioners, paediatricians, ENT specialists and Allergists collaborate in providing optimal and cost effective patient care. The optimal setting for such a network is the Allergy Centre. Notably when the atopic patient is suffering from several allergic diseases such as eczema, asthma, food allergy next to AR referral to an allergy centre is rational and cost effective.

Next to other specialists, Allergists play their role within this framework, notably by testing counselling and treating patients with complex multi-organ allergies. The Allergy Centre offers to private allergists, GPs and other medical specialists more extensive diagnostic and therapeutic possibilities. The Allergy Centre can also offer care and education through nurses, dieticians and other health care workers. The optimal location for an Allergy Centre is in a university hospital or a large regional hospital, where all relevant specialties are adequately represented.

In addition, most health care systems consider continuing medical education a potential tool to improve quality of care and reduce disease management costs. The effectiveness of a one-year continuing medical education/continuing professional development course for general practitioners, regarding the improvement in knowledge of ARIA and GINA guidelines and compliance with them in asthma management was proven recently.

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15 WEB-BASED SURVEYS AND MONITORING IN THE MANAGEMENT OF ALLERGIC RHINITIS AND CHRONIC RHINOSINUSITIS

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KEY MESSAGES

- Over the last two decades Internet has become an important source of information
- Online tools can provide feedback about real life and on real time and have potential predictive use
- Recently, online tools have been employed to diagnose and treat minor symptoms
- Online surveys are easy, inexpensive and convenient tools to reach large number of responders
- In cases of patients with limited access to Internet potential bias in collected information can rise

The use of Internet in Medicine has a great potential for interventions that are just beginning to appear. The knowledge of Google trends offers data regarding the epidemiology of rhinitis. Google searches of the term allergic rhinitis (AR) have a clear seasonality, with peaks during spring and late summer, and with patterns that differ between the North and South hemisphere (Figure 1). They closely correlate with searches on pollen counts, and information about antihistamines, as well as with records of antihistamine sales, and thus reflect the suffering caused by the disease in real time. They have a potential use to predict and monitor outbreaks of AR, similar to other diseases such as influenza.

As part of the epidemiologic research, online surveys are currently easy to prepare and require a limited time to upload the survey, while responses are collected directly in a database-format ready to be analysed without further management. Another great advantage of online surveys is that they can reach a huge number of potential participants. Survey Monkey and Google drive are two extensively used examples of such online survey tools. Surveys can be dedicated to specific diseases, or can render information as part of more general approaches to health conditions. Online surveys addressing topics on rhinitis or chronic rhinosinusitis (CRS) have been able to identify associations of AR with sleep time and duration as well as with depression and suicidal ideation. They furthermore provide data to compare the quality of life between patients with AR and those with CRS, to check the impact of rhinitis symptoms according to their type or time of onset and to identify unmet treatment needs. There are, however, limitations in the usefulness of online-collected information, as younger patients (Figure 2) and those with more severe symptoms might be more likely to use the web to receive information or advice and to participate in online surveys. Nonetheless, concerns about the reliability and comparability of answers are usually present in relation to more traditional sources of information too.

The Internet also offers interactive questionnaires in several languages for the patients to assess their rhinitis severity and control according to e.g. the ARIA classification (Figure 3). Depending on the answers provided the patients can reach a recommendation at the end of some of these questionnaires. Tailored, rather than static, information seems to work better by enabling patients to

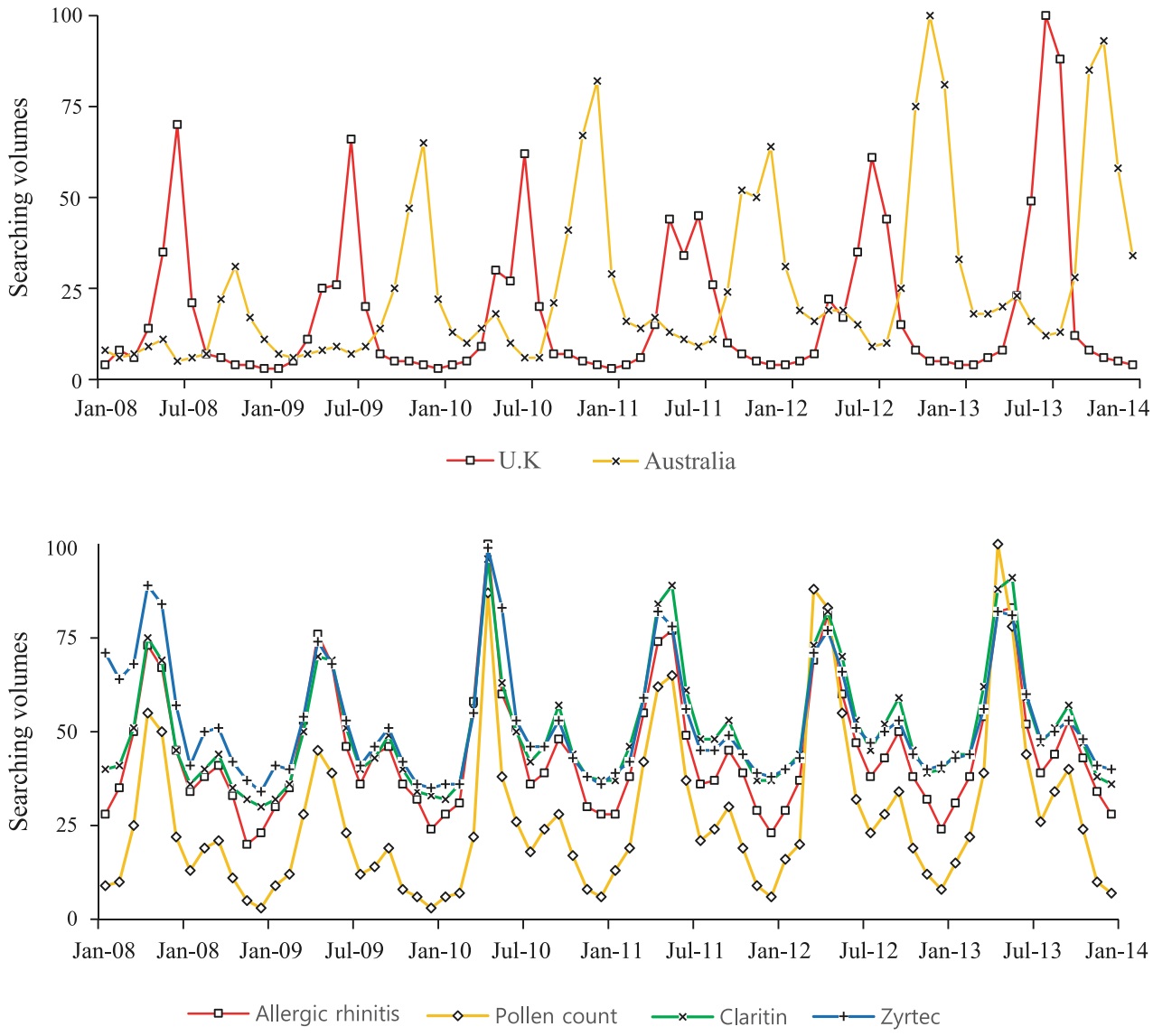

Figure 1 Seasonality of Google searches on allergic rhinitis, with distinct patterns for the North and the South hemisphere. The searches in the US on related topics as pollen count or antihistamines follow the same pattern and reflect symptoms ((*Reproduced with permission from Kang MG, Song WJ, Choi S, et al. Google unveils a glimpse of allergic rhinitis in the real world. Allergy 2015;70:124-128, with permission from Willey Blackwell.*)

Figure 2 The digital breach can cause an overrepresentation of younger generations in the information collected online.

manage minor symptoms in certain diseases, and could also prove useful in cases of mild rhinitis.

In conclusion, even though current data on the usefulness of web-based tools regarding the management of AR and CRS are still preliminary, they can be considered promising. With the constant progress of online technologies further improvement is expected which will assist physicians and patients in the decision-making process.

Figure 3 Online questionnaire of the ARIA initiative for the evaluation of respiratory health. http://www.whiar.org/Questionnaire.php

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16 VISION, ROADMAP AND LAND-MARKING EVENT

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The World Health Organization declares chronic respiratory diseases as one of the four major health problems of mankind. The prevalence of allergic rhinitis (AR) has steadily increased over the past decades, affecting up to 30% of children and adults in Europe. A large-scale European survey has demonstrated chronic rhinosinusitis (CRS) is affecting 11% of the total European population. The socio-economic impact of chronic upper airway inflammation cannot be underestimated. Direct and indirect costs of chronic rhinitis and rhinosinusitis sum up to more than 150 billion Euros per year in Europe. In addition, up to 20% of patients treated for AR and CRS remain uncontrolled, even despite surgery for CRS. Given the fact that AR is a major risk factor for the development of asthma, action should be undertaken to prevent asthma.

KEY MESSAGES

- Allergy epidemic affects more than one billion patients with a Global rise in prevalence, which may reach up to 4 billion affected individuals in 2050. Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) affect more than 30% of the population worldwide
- Both AR and CRS are inflammatory conditions with a significant degree of uncontrolled disease, even despite surgery in CRS
- The already existing many unmet needs and the huge socioeconomic burden for the health care systems are expected to substantially increase
- The socio-economic impact of chronic upper airway diseases is estimated for Europe at above 150 billion Euros per year.
- Effective policies and strategy development are needed at the global, regional and national level
- Efforts to overcome unmet needs should focus on 4 main directions:
  - Intensive research and development
  - Improved patient care at the global level
  - Increased public awareness
  - Upgrade of the Allergy domain in the political agenda
- A "Global Allergy Fight Strategy" should be developed:
  - All stakeholders should be involved
  - A multidisciplinary and scientific approach should be used
  - Next generation guidelines should be developed
  - World Respiratory Centers and Integrated Surveillance Networks should be established

UNMET NEEDS

Unmet needs in the field of AR and CRS can arbitrarily be split into four different domains: education, research, development and clinical care.

In view of the major problem of underdiagnosis of AR and CRS, a higher level of **education** of physicians, pharmacists and patients is warranted, focusing on the benefits of proper diagnosis and adequate personalized treatment. Benefits of this approach can be evaluated from the patient perspective, with improved quality of life (QoL) by reduced symptoms or cure from disease, as well as from a society perspective by a significant reduction of socio-economic impact of chronic upper airway disease and even prevention of asthma.

Figure 1 Joining forces by all stakeholders in a unique platform is necessary to reach the goal of tacking the burden of chronic inflammatory upper airways diseases.

Given the lack of insight into factors driving uncontrolled upper airway disease, **research** should focus on determinants of uncontrolled AR and CRS, including severe chronic airway disease (SCUAD). Better insight into the exogenous and endogenous factors being responsible for uncontrolled disease will allow the design of optimal treatment strategies.

The **development** of novel tools for evaluation of subjective burden of the disease by the patients are needed, like user-friendly and cheap devices for the measurement of nasal patency, hyperreactivity and inflammation, smell dysfunction and control of disease. The daily follow-up of symptom control and other parameters of the disease need to be implemented in routine care, as this will help both the patients and physicians to design optimal personalized care.

Current **clinical care** pathways should be optimized and personalized for obtaining a higher degree of control for both AR as well as CRS. In AR, an action plan is needed to improve endotyping, predict the success of different medical treatment options, and prevent the development of asthma. In CRS, the choice of prolonged medical treatment or surgery needs to be based on the prediction of success of both approaches and the patients' preference in this regard. In CRS without nasal polyps (CRSsNP), personalized care is warranted with improvement of insight into the different factors of the pathophysiology and better drug delivery at the site of inflammation. In CRS with nasal polyps (CRSwNP), novel biologicals are emerging as effective treatment options for those patients not responding well to current medical or surgical treatment. The precise positioning of biologicals into existing care pathways for CRS remains the challenge, as they may represent an alternative for surgery. Given the persistence of inflammation after surgery (FESS) in the majority of patients, post-operative prolonged care and follow-up is mandatory.

A WORLDWIDE STRATEGY TO REDUCE THE BURDEN OF CHRONIC UPPER AIRWAY DISEASE

In view of the high need to optimize patient care in the epidemic of chronic upper airway diseases, a worldwide strategy to reduce the burden of chronic upper airway disease is warranted. This action plan can only be successful by the combined actions of all the stakeholders: physicians and other healthcare professionals such as allied health and pharmacists, researchers, patient organizations, industry and policy makers. Therefore, joining forces by all stakeholders in a unique platform will be necessary to reach the goal (Figure 1).

Research and development should be synergized and prioritized in order to achieve sustainable results on prevention, biomarkers, curative treatment, anti-viral vaccines, and novel drug development. There are a number of barriers and obstacles in grant giving bodies to be solved, particularly to support human immunology and allergy research (Table 1).

A WORLDWIDE STRATEGY TO FIGHT AND MANAGE ALLERGIC DISEASES SHOULD BE DEVELOPED (TABLE 2).

All stakeholders including healthcare professionals, psychologists, patient organizations, educators, industry, and policy makers should be involved. A multidisciplinary and scientific approach is essential. Modern global guidelines should be developed and implemented for the management of AR, CRS and co-morbidities. The new generation guidelines should provide structured, multidisciplinary, region and environment-oriented and individual patient-focused solutions, with full considerations on differences across cultures. A good move forward is the current concept of integrated care pathways for reaching an optimal therapeutic approach in patients with AR (Figure 2). It is now time to act on an integrated care platform for chronic airway disease.

TABLE 1

Obstacles in allergy, rhinitis and rhinisinusitis research
• Lack of political awareness and low understanding and priority setting for the allergy epidemics
• Curative approaches and research for prevention has not been so far efficiently supported
• Small quantities of grants have been given to hypothesis-based research, although the real need is for large scale, non hypothesis based, in dept research, which is now possible with the novel developments in next generation DNA and RNA sequencing, exposome and epigenetic analysis and biomarkers
• Human research is receiving relatively less funding in many grant giving bodies compared to animal models
• Many major grant giving bodies had to decrease their budgets because of economical conditions in many countries

TABLE 2

Global allergy fight strategy
• Accept allergies as a Global Public Health Problem
• Upgrade "Allergy" on the political agenda
• Perform research and develop strategies to reduce risk factors
• Acknowledge the role of primary care, allied health personnel and pharmacists as the central link between patients and physicians and initiate global education programmes
• Develop intensive public education and awareness programmes
• Increase research funds in general
• Prioritize prevention and curative treatments
• Generate resources for prevention and control
• Strengthen the specialty of "Allergology"
• Harmonize and economize the educational and awareness activities of all stakeholders

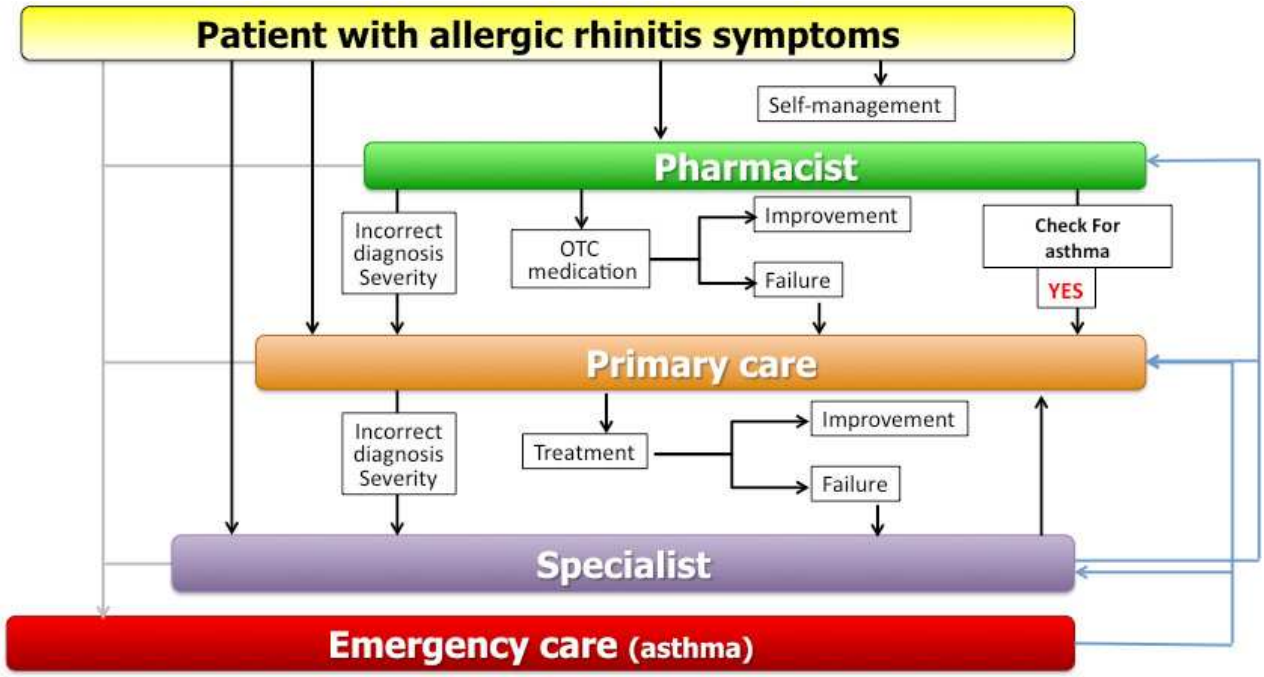

Figure 2 The concept of integrated care pathways for reaching an optimal therapeutic approach in patients with allergic rhinitis. (*From Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs)., Eur Respir J 2014 Aug;44:304-23.*)

The European Academy of Allergy and Clinical Immunology (EAACI) is a non-profit organization active in the field of allergic and immunologic diseases such as asthma, rhinitis, eczema, occupational allergy, food and drug allergy and anaphylaxis. Its scope covers both basic science and clinical medicine.

Since its establishment in 1956, EAACI has grown to become the largest medical association in Europe in the field of allergy and clinical immunology. Its membership currently includes nearly 7800 members from 121 countries, representing academicians, clinicians, and allied health professionals. In addition, EAACI includes 47 National Allergy Societies as members.

EAACI's mission is to provide the most efficient platform for scientific communication and education in the field of allergy and immunology, ultimately striving to ease the lives of patients suffering from these diseases. EAACI is regarded as the **primary source of expertise** in Europe for all aspects of allergy.

EAACI's activities

- Fostering science through dedicated platforms Annual Congress, Focused Meetings, Guidelines and Position Papers
- Educating professionals (Allergy Schools; CME system; knowledge examination in allergy and clinical Immunology; Research and Clinical Fellowships)
- Disseminating knowledge through EAACI Journals (Allergy, Pediatric Allergy Immunology, Clinical and Translational Allergy, EAACI Newletter) and online communication platforms
- Advocating change and raising awareness among the European Union's decision makers about the importance of allergy and clinical immunology and the opportunities to prevent and treat allergies through *Public Campaigns* and *Public Declarations*

Allergic rhinitis (AR) and chronic rhinosinusitis (CRS) affect more than 30% of the population worldwide and pose a huge burden on healthcare systems through direct and indirect costs. The European Academy of Allergy and Clinical Immunology called on all worldwide leaders to develop the "Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis"

The EAACI Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis was written by 218 authors from 38 countries and aims to increase awareness on the global epidemic and the burden of chronic inflammatory upper airways diseases and to warrant their recognition as a main concern in national health strategies.

Several priorities can be identified such as the development of novel tools for evaluation of subjective burden of the disease by the patients, improvement of the current clinical care pathways to obtaining a higher degree of control, research focused on determinants of uncontrolled and severe AR and CRS, altogether with a higher level of education of physicians, pharmacists and patients focusing on the benefits of proper diagnosis and adequate personalized treatment.

In view of the high need to optimize patient care in the epidemic of chronic upper airway diseases, a worldwide strategy to reduce the burden of chronic upper airway disease is warranted.

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